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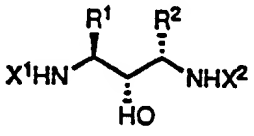

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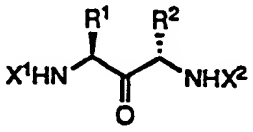

(II)

(57) Abstract

C mpounds useful as inhibitors of retroviral proteases characterized by structures (I) and (II) wherein the X^1 and X^2 groups may consist f 0 to 2 α-amino acid groups terminally substituted by hydrogen or one of a number f end groups, and the R^1 and R^2 group can be selected from a wide variety f hydrocarb n radicals.

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TITLE

RETROVIRAL PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

This invention relates to compounds which are inhibitors of aspartic proteases, particularly of retroviruses.

Retroviruses, that is, viruses within the family of Retroviridae, are a class of viruses which transport their genetic material as ribonucleic acid rather than deoxyribonucleic acid. Also known as RNA-tumor viruses, their presence has been associated with a wide range of diseases in humans and animals. They are believed to be the causative agents in pathological states associated with infection by Rous sarcoma virus (RSV), murine leukemia virus (MLV), mouse mammary tumor virus (MMTV), feline leukemia virus (FeLV), bovine leukemia virus (BLV), Mason-Pfizer monkey virus (MPMV), simian sarcoma virus (SSV), simian acquired immunodeficiency syndrome (SAIDS), human T-lymphotropic virus (HTLV-I, -II) and human immunodeficiency virus (HIV-l, HIV-2), which is the etiologic agent of AIDS (acquired immunodeficiency syndrome) and AIDS related complexes, and many others. Although the pathogens have, in many of these cases, been isolated, no satisfactory method for treating this type of infection has been developed. Among these viruses, the HTLV and HIV have been especially well characterized.

Critical to the replication of retroviruses is the production of functional viral proteins. Protein synthesis is accomplished by translation of the open reading frames into polyprotein constructs, corresponding to the gag, pol and env reading frames. The gag and pol precursor proteins, are processed by a viral protease into the functional proteins. The

HIV-1 protease has been classified as an aspartic acid protease (Meek et al., Proc. Natl. Acad. Sci. USA, 88, 1841 (1989)). The proteolytic activity provided by the viral protease in processing the polyproteins cannot be provided by the host and is essential to the life cycle of the retrovirus. In fact, it has been demonstrated that retroviruses which lack the protease or contain a mutated form of it, lack infectivity. See Katoh et al., Virology, 145, 280-92(1985), Crawford, et al., J. Virol., 53, 899-907(1985), Debouck, et al., Proc. Natl. Acad. Sci. USA, 84, 8903-6(1987). Inhibition of retroviral protease, therefore, presents a method of therapy for retroviral disease.

Methods to express retroviral proteases in E. coli have been disclosed (Debouck, et al., Proc. Natl. Acad. Sci. USA, 8903-06(1987) and Tomasselli et al., Biochemistry, 29, 264-9 (1990) and refs. therein).

Inhibitors of recombinant HIV protease have been reported (Dreyer et al., Proc. Natl. Acad. Sci. USA, 86, 9752-56 (1989); Tomasselli et al. supra; Roberts et al., Science, 248, 358 (1990); Rich et al., J. Med. Chem., 33, 1285-88 (1990); Sigal et al., Eur. Pat. Appl. No. 337 714; Dreyer et al. Eur. Pat. Appl. No. 352 000). Moreover, certain of these inhibitors have been shown to be potent inhibitors of viral proteolytic processing in cultures of HIV-1 infected T-lymphocytes (Meek et al., Nature (London), 343, 90 (1990) and by Roberts et al. supra).

The limitations of current strategies for aspartic protease inhibition include (1) oral bioavailability; (2) plasma clearance lifetimes (e.g., through biliary excretion or degradation); (3) selectivity of inhibition; and (4) in the case of intracellular targets, membrane permeability or cellular uptake. The present invention relates to a new inhibitors of retroviral and aspartic proteases. Unlike previously described inhibitors , the compounds of this invention are not analogues of peptide substrates possessing a scissile dipeptide mimetic. They also deviate substantially from peptide substrate-like structure in that they do not possess a conventional amino-to-carboxyl terminus orientation.

SUMMARY OF THE INVENTION

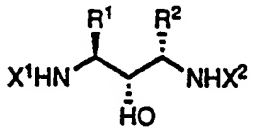
This invention comprises compounds having the structures particularly pointed out in the claims and described hereinafter which bind to retroviral proteases. These compounds are inhibitors of viral protease and are useful for treating disease related to infection by viruses.

This invention is also a pharmaceutical composition, which comprises an aforementioned compound and a pharmaceutically acceptable carrier therefor.

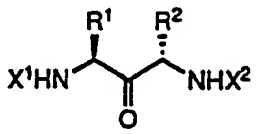
This invention further constitutes a method for treating viral diseases, which comprises administering to a mammal in need thereof an effective amount of an aforementioned inhibitor compound.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention have the structure I or II:



I



II

wherein X^1 and X^2 are the same or different and are A-$(B)_n$- where n = 0-2; and

B is, independently, an α-amino acid chosen from the group: Ala, Asn, Cys, Trp, Gly, Gln, Ile, Leu, Met, Phe, Pro, Ser, Thr, Tyr, Val, His, or trifluoroalanine, wherein the amino group of B is bonded to A or the carboxy group of the adjacent residue B, whichever is appropriate, and the carboxy group of B is bonded to the amino group of the adjacent residue B or I or II, whichever is appropriate; and

A is covalently attached to the amine group of the adjacent residue B or to the amine group of I or II if n=0, and is:

1) trityl,
2) hydrogen,
3) C_1-C_6 alkyl,
4) R^3-CO- wherein R^3 is:
   a) hydrogen,
   b) C_1 - C_6 alkyl, unsubstituted or substituted with one or more hydroxyl groups, chlorine atoms, or fluorine atoms,
   c) phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4, wherein R^4 is:
      i) C_1 - C_4 alkyl,
      ii) halogen, whrein halogen is F, Cl, Br or I,
      iii) hydroxyl,
      iv) nitro,
      v) C_1 - C_3 alkoxy, or
      i) -CO-N$(R^{10})_2$ wherein R^{10} is, independently, H or C_1-C_4 alkyl;
   d) a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazolyl;
5) phthaloyl wherein the aromatic ring is unsubstituted or substituted with one or more substitutents R^4
6) $R^5(R^6R^7C)_m$-CO- wherein m = 1-3 and R^5, R^6, and R^7 are independently:
   a) hydrogen,
   b) chlorine or fluorine,
   c) C_1 - C_3 alkyl unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups,

d) hydroxyl,

e) phenyl or naphthyl unsubstituted or substituted with one or more substitutents R^4,

f) C_1 - C_4 alkoxy,

g) a 5-7 member heterocycle,

h) R^5, R^6, and R^7 may be independently joined to form a monocyclic, bicyclic, or tricyclic ring system each ring of which is C_3-C_6 cycloalkyl;

7) $R^5(R^6R^7C)_mW$- wherein m = 1-3 and W is OCO or SO_2 and R^5, R^6, and R^7 are as defined above, except R^5, R^6, and R^7 are not chlorine, fluorine or hydroxyl if they are adjacent to W;

8) R^8-W- wherein R^8 is a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazoyl;

9) R^9-W- wherein R^9 is phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4;

10) R^5-$(R^6R^7C)_m$-P(O)(OR^{11})- wherein R^{11} is C_1 - C_4 alkyl or phenyl;

11) R^8-P(O)(OR^{11})-; or

12) R^9-P(O)(OR^{11})-;

R^1 and R^2 are the same or different and are:

1) $-CH_2R^{12}$ wherein R^{12} is

a) NH-A wherein A is defined as above;

b) R^5-$(R^6R^7C)_m$-;

c) R^5-$(R^6R^7C)_mV$- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-$(R^6R^7C)_m$-$S(O)_n$- wherein m = 1-3 and n = 0-2 and R^5, R^6, and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacen to sulfur,

e) R^8-$S(O)_n$-,

f) R^9-$S(O)_n$-,

g) $(R^{13}O)P(O)(OR^{14})$- wherein R^{13} and R^{14} are, independently:

i) C_1 - C_6 alkyl,

ii) C_3 - C_6 cycloalkyl,

iii) H,

iv) R^9,

v) R^8,

h) $R^{13}P(O)(OR^{14})$-,

i) $N(R^{10})_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogenous heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl,

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C_1 - C_6 alkyl,

ii) R^9,

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH_2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-Benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2 - C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2 - C_6 alkenyl, optinally substituted with one or more gropus R^9;

2) hydrogen,

3) C_1 - C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups,

4) C_3 - C_7 cycloalkyl; and pharmaceutically acceptable salts thereof.

Peptide compounds of the foregoing description are preferred which are C2 symmetric wherein $X^1=X^2$, and $R_1=R_2$.

Suitably the compound has structure I and R^1 - R^2 and $X^1 = X^2$.

Suitably R^1 and R^2 are C_1-C_6alkyl. Preferably R^1 and R^2 are benzyl.

Suitably X1 and X2 are AlaAla, Val, Cbz-Val, Cbz or hydrogen. Preferably X^1 and X^2 are Cbz-Val.

The compounds of this invention are useful in the manufacture of a medicament, in particular, for a medicament for treating infection by retroviruses.

C_2 symmetric peptide compounds wherein R_1 and R_2 are C_1-C_6 alkyl or aralkyl and X^1 and X^2 are single amino acids or mono- or dipeptides; these groups may be terminally substituted by common acyl groups or blocking groups commonly used in peptide synthesis, such as t-Boc or Cbz, are also preferred.

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the parent drug.

As used herein except where noted, the term "alkyl" refers to a straight or branched chain alkyl radical of the indicated number of carbon atoms including, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl, and the like; "alkoxy" represents an alkyl group of the indicated number of carbon atoms attached through a bridging oxygen atom; "cycloalkyl" is intended to include staurated ring groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; "alkenyl" is meant to include either straight or branched hydrocarbon chains containing one or more carbon-carbon double bonds which may occur at any stable point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, 2-methyl propenyl, and the like; "alkynyl" refers to either a straight or branched hydrocarbon chain or the indicated number of carbon atoms which contains a carbon-carbon triple bond which may occur at any stable piont along the chain, such as ethylyl, 2-propynyl, 2-butynyl, 4-pentynyl, 2-methyl-3-propynyl, and the like.

As used herein except where noted, the term "heterocycle" represents a stable 5- to 7-membered mono- or bicyclic heterocyclic ring, which is either satureated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, I and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic rings may be attached to any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements including piperidinyl, piperazinyl, 2-oxopinerazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, prydiazinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazoyly, furyl, tetrahydrofuryl, tetrahydrophyranyl, thienyl, thiamorpholinyl sulfoxide, thiamorpholinyl sufone, and oxadiazolyl.

When any variable (e.g., A, B, R^1, R^2, R^3, ..., R^{17}, heterocycle, substituted phenyl, etc.) occurs more than one time in any constituent or in formula I or II, its definition on each occurence is independent of its definition at every other occurence. Also, combination of substituents and/or variables are permissible only if such combinations result in stable compounds. By convention used herein, a geminal diol, for example when R6 and R7 are simultaneiously hydrowyl, is meant to be equivalent with a carbon-oxygen double bond.

Other abbreviations and symbols commonly used in the art used herein to describe the peptides include the following:

Amino acid	three letter code	Amino acid	three letter code
Alanine	Ala	Leucine	Leu
Arginine	Arg	Lysine	Lys
Asparagine	Asn	Methionine	Met
Aspartic Acid	Asp	Phenylalanine	Phe
Cysteine	Cys	Proline	Pro
Glutamine	Gln	Serine	Ser
Glutaminic Acid	Glu	Threonine	Thr
Glycine	Gly	Tryptophan	Trp
Histidine	His	Tyrosine	Tyr
Isoleucine	Ile	Valine	Val
Asparagine or Aspartic Acid			Asx
Glutamine or Glutamic Acid			Glx

In accordance with conventional representation, the amino terminus is on the left and the carboxy terminus is on the right. All chiral amino acids (AA) can occur as racemates, racemic mixtures, or individual enantiomers or diasteriomers, with all isomeric forms being included in the present invention. β-Ala refers to 3-amino propanoic acid. Boc refers to the t-butyloxycarbonyl radical, Cbz refers to the carbobenzyloxy radical, i-Bu refers to isobutyl, Ac refers to the acetyl, Ph refers to phenyl, DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, HOBT refers to 1-hydroxybenzotriazole, NMM is N-methylmorpholine, DTT is dithiothreitol, EDTA is ethylenediamine tetraacetic acid, DIEA is diisopropyl ethylamine, DBU is 1, 8 diazobicyclo [5.4.0] undec-7-ene, DMSO is dimethylsulfoxide, DMF is dimethyl formamide and THF is tetrahydrofuran. HF refers to hydrofluoric acid and TFA refers to trifluoroacetic acid.

The peptide moieties denoted by X^1 and X^2 are generally dipeptides or smaller. However, longer peptides which encompass the residues defined herein are also believed to be active and are considered within the scope of this invention.

The selection of residues or end groups may be used to confer favorable biochemical or physico-chemical properties to the compound. The use of hydrophilic residues may be used to confer desirable solubility properties or D-amino acids at the carboxy terminus may be used to confer resistance to exopeptidases.

Synthesis of componds I in which $R^1 = R^{12}CH_2$, $R^1 = R^2$, and $X^1 = X^2$ is achieved from D-(+)-arabitol (Schemes 1-2). Thus, D-(+)-arabitol is converted to 1,2:4,5-Dianhydro-3-(O-benzyl)-D-(+)-arabitol (10) as described by S.L. Schreiber, T. Samnakia and D.E. Uehling, J. Org. Chem. 54, 15-16 (1989). The diepoxide 10 can then be reacted with NaN_3 in DMF to provide the resulting dihydroxy terminal diazide, which is converted to the protected diaziridine, 1.2:4,5-Di-(N-benzyloxycarbonylimino)-3-(O-benzyl)pentanol, by dimesylation of the dihydroxy terminal diazide followed by reduction with $LiAlH_4$ with

concommitant diaziridine formation followed by reaction with benzylchloroformate. The resulting diaziridine is reacted with appropriate nucleophiles such as $(CH_3)_2CuLi$, to introduce the side-chain groups R^1 (Scheme 1). This procedure is especially suited to the preparation of compound I where $R^1 = CH_2R^{12}$ where R^{12} is hydrogen or is a group that forms a stable and reactive cuprate reagent, such as methyl, butyl, isopropyl, or other alkyl, alkenyl or aryl which is optionally substituted, for example with fluorine or alkoxy or protected hydroxyl.

Alternatively, compounds represented by formula I in which $R^1 = R^{12}CH_2$, $R^1 = R^2$, and $X^1 = X^2$ can be prepared from the diepoxide **10** by reaction with appropriate carbon nucleophiles such as cuprate reagents $(R^{12})_2CuLi$ or alkynylaluminum reagents to introduce the side-chain groups R^1 (Scheme 2). This procedure is also especially suited to the preparation of compound I where $R^1 = CH_2R^{12}$ where R^{12} is a group that forms a stable and reactive cuprate reagent, as described above. The resulting diol product is converted to the corresponding diamine with inversion of configuration at the alcohol carbons. One way in which this is accomplished is via conversion of the diol to the dimesylate, by reaction with methanesulfonyl chloride and triethylamine, followed by displacement with NaN_3 in DMF to provide the substituted 2,4-diazido-3-benzyloxypentane; conversion to the 2,4-diamino derivative follows by reduction with a hydride reagent such as $LiAlH_4$ or by catalytic hydrogenation with a catalyst such as Pd(O) or Raney-Ni to provide the core structure I (Scheme 2). Introduction of the groups $X^1 = X^2$ is accomplished by standard condensation reactions as are well known in the art.

Compound I in which R^{12} is NH-A can be prepared from the diepoxide **10** by reaction with NaN_3 in DMF to provide the resulting dihydroxy terminal diazide, which is converted to the corresponding tetraazide with inversion of configuration at the alcohol carbons as described above, and subsequently to the corresponding tetraamine. Selective reaction of the terminal amines with groups A or with protecting groups such as Boc or Cbz is then followed by introdution of the groups $X^1 = X^2$. In a related fashion, groups $R^1 = R^2$ in compounds I in which R^1 is $N(R^{10})_2$, $NR^{15}R^{16}$, $R^5\text{-}(R^6R^7C)_mV\text{-}$ or $R^5(R^6R^7C)_m\text{-}S(O)_n\text{-}$ can be introduced by reaction of diepoxide **10** with the appropriate oxygen, nitrogen, or thiol nucleophile, with subsequent thiol oxidation as necessary; reaction of diepoxide **10** with the appropriate phosphorus nucleophile in an Arbuzov or Michaelis-Arbuzov reaction allows introduction of gropus $R^1 = R^2$ which are $(R^{13}O)P(O)(OR^{14})\text{-}$ or $R^{13}P(O)(OR^{14})\text{-}$.

Alternatively, compounds represented by I can be prepared from protected alpha-amino aldehydes $P^2NHCH(R^1)CHO$. The required N-protected alpha-amino aldehydes are readily prepared from the respective N-protected alpha-amino acids $P^2NHCH(R^1)CO_2H$, for example by reduction of the corresponiding esters with diisobutyl aluminum hydride, by

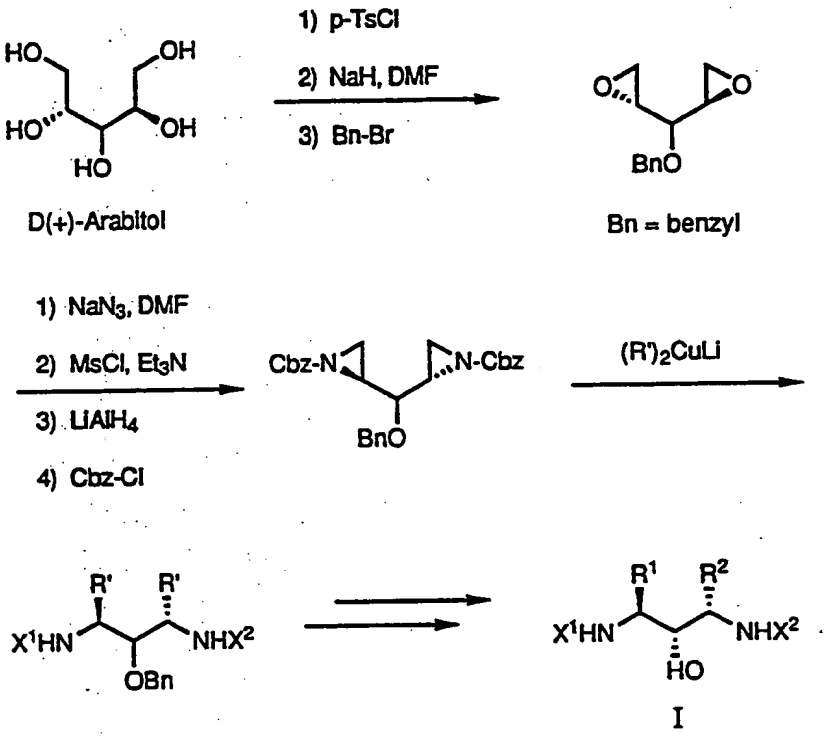
reduction of the derived N-methyl, N-methoxy amides $P^2NHCH(R^1)CONme(OMe)$ with $LiAlH_4$ (Fehrentz and Castro, Synthesis 676 (1983)), or by reduction to the N-protected alpha-amino alcohol followed by oxidation with DMSO-$(COCl)_2$ or SO_3-pyridine (Review: Jurczak and Golebiowski, Chem Rev. 89, 149 (1989)). Generally the amino protecting group, P^2, is t-Boc-, Cbz-, p-toluenesulfonyl or another standard protecting group chosen as well known in the peptide art. The synthesis of I proceeds via preparation of an intermediate $P^2NH(R^1)CH(OH)CH(R^2)COQ$ by aldol condensation with an acyl derivative, R^2CH_2COQ, under the conditions of Evans et al. (Evans, Ennis and Mathre, J. Am. Chem. Soc. 104, 1737-39 (1982); Review: Evans, Nelson and Taber, in Topics in Stereochemistry, Vol. 13; Allinger, Eliel, Wilen, eds.; Wiley, 1982; pp 1-114.), where Q is a chiral auxiliary used to direct the stereochemical outcome of the aldol reaction and is often the oxazolidinone derived from valinol, norephedrine, or phenylalanol. Hydroxyl protection with a protecting group P^1 such as TBDMS or benzyl and subsequent hydrolytic removal of the group Q yields the intermediate $P^2NH(R^1)CH(OP^1)CH(R^2)CO_2H$, which is subjected to Curtius rearrangement (Reviews: Banthorpe, in Patai, "The Chemistry of the Azido Group." pp. 397-405, Interscience Publishers, NY, 1971; Smith, Org. React. 3, 337-449 (1946)) to provide the compound $P^2NH(R^1)CH(OP^1)CH(R^2)NH_2$ which is an unsymmetrically protected form of I. This route is versatile in that it allows access to all steroisomers of compounds I and to unsymmetrical compounds I, in which R^1, R^2 are different and X^1, X^2 are different.

Synthesis of compounds represented by formula II is achieved by oxidation of the central hydroxyl group within the corresponding compounds I, as is well known in the art. Useful oxidation reagents include, but are not limited to, Jones Reagent, $(COCl)_2$-DMSO, pyridinium dichromate, and pyridinium chlorochromate.

Either enantiomer of compounds of structures I and II can be prepared from the respective enantiomer of arabitol by the procedures shown in Schemes 1-2.

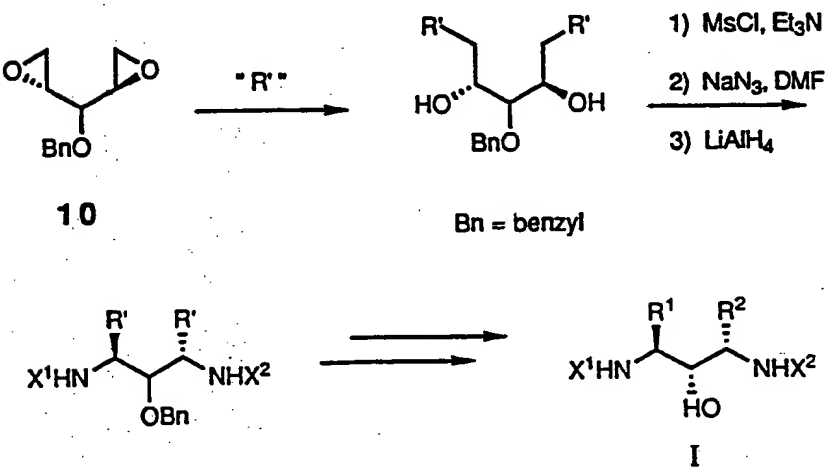
Scheme 1

Synthesis of I

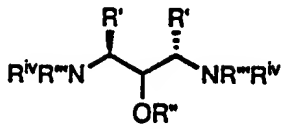


Scheme 2

Synthesis of I



Accordingly, in another aspect, this inventi n is a process for preparing a compound of the formula:



wherein R' is

1) a) NH-A wherein A, R^5- R^{10} and m are as defined for formula I;

b) R^5-($R^6R^7C)_m$-;

c) R^5-($R^6R^7C)_m$ V- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-($R^6R^7C)_m$-S- wherein m = 1-3, and R^5, R^6, and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to sulfur,

e) R^8-S-,

f) R^9-S-,

g) (R^{13}O)P(O)(OR^{14})- wherein R^{13} and R^{14} are, independently:

i) C_1-C_6 alkyl,

ii) C_3-C_6 cycloalkyl,

iii) H,

iv) R^9, or

v) R^8,

h) R^{13}P(O)(OR^{14})-,

i) N(R^{10})$_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogens heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl, or

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C^1-C^6 alkyl,

ii) R^9, or

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2-C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2-C_6 alkenyl, optionally substituted with one or more groups R^9;

2) hydrogen,

3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups, or

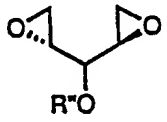
4) C_3-C_7 cycloalkyl,

R" is a hydroxyl protecting group, and

R"' and R'' are hydrogen, an amino-protecting group or taken together are N_2,

which comprises

1) reacting a compound of the formula:



with a compound R'-Z, wherein Z is a moiety which renders R' nucleophilic, and R" is a hydroxyl protecting group,

2) converting the resulting hydroxy groups to displaceable groups,

3) reacting the displaceable groups with a nitrogen nucleophile.

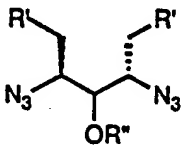
Hydroxyl protecting groups are those groups which are commonly used in the art to mask the reactivity of the hydroxyl group, while also capable of being selectively removed to regenerate the hydroxyl group. Typically, the oxygen-hydrogen bond is replaced by an oxygen-carbon bond. Useful hydroxyl protecting groups are described in Greene, T.W., Protective Groups in Organic Synthesis, John Wiley & Sons, New York (1981), but many others are well known in the art. The arylmethyl ethers, substituted or unsubstituted, are one particularly useful class of groups for protecting the hydroxyl group. The benzyl protecting group, optionally with substituents upon the aryl ring, is useful.

Typically Z is hydrogen, an alkali metal, such as Li, Na or K, or an earth metal, such as magnesium, or a transition metal, such as copper, aluminum, titanium, zinc or cadmium, or a species derived therefrom. Representative of R'-Z are optionally substituted alkyl, aryl or heteroaryl lithium, alkyl, aryl or heteroaryl magnesium halides (eg. Grignard reagents), lithium dialkyl cuprate, lithium diaryl cuprate, or the alkali metal salts of optionally substituted alkyl alcohols, phenols or benzyl alcohols. Lithium diphenyl cuprate is especially useful.

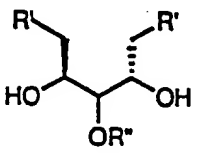
The hydroxyls are converted to suitable displaceable groups, such as mesylate, tosylate, brosylate, benzoate, acetate and halide, by methods common in the art. The tosyl group is especially suitable and is formed by reacting the hydroxyl groups with tosyl chloride, for instance.

Suitable nitrogen nucleophiles are those which are able to react with a displaceble group. Unhindered organic amines or heterocyles, metal salts of amines, heterocycles or azide are useful. Generally an nitrogen containing group of the formula R'''R''''N-Z, wherein Z is as defined above and R''' and R'''' are hydrogen, an amino-protecting group or taken together are N_2 (eg. azide) are useful. A metal azide, such as sodium or potassium azide, is preferable. Subsequent reduction of the azido groups provides amino groups.

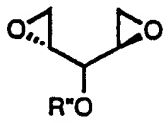
Particularly useful intermediate compounds of this invention are:



III



IV



V

wherein R' and R" are as defined above.

The compounds of this invention are prepared by the solid phase technique of Merrifield (J. Am. Chem. Soc., 85, 2149 (1964), or preferably by solution methods known to the art. A combination of solid phase and solution synthesis may be used, as in a convergent synthesis in which di-, tri-, or tetra-peptide fragments may be prepared by solid phase synthesis and either coupled or further modified by solution synthesis. The methods of peptide synthesis generally set forth in J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", Pierce Chemical Company, Rockford, Il (1984) or M. Bodonsky, Y.A. Klauser and M. A. Ondetti, "Peptide Synthesis", John Wiley & Sons, Inc., New York, N.Y. (1976), or "The Peptides" gross and Meienhoffer, eds.; Acad. Press, 1979, Vols I-III, may be used to produce the peptides of this invention and are incorporated herein by reference.

Each amino acid or peptide is suitably protected as known in the peptide art. For example, the Boc- or carbobenzyloxy-group is preferred for protection of the amino group, especially at the α position. A benzyl group or suitable substituted benzyl group is used to protect the mercapto group of cysteine, or other thiol containing amino acids; or the hydroxyl of serine or threonine. The tosyl or nitro group may be used for protection of the guanidine of Arg or the imidazole of His, and a suitably substituted carbobenzyloxy group or benzyl group may be used for the hydroxyl group of Tyr, Ser or Thr, or the ε-amino group of lysine. Suitable substitution of the carbobenzyloxy or benzyl protecting groups is ortho and/or para substitution with chloro, bromo, nitro or methyl, and is used to modify

the reactivity of the protective group. Cysteine and other sulfur-containing amino acids may also be protected by formation of a disulfide with a thioalkyl r thioaryl group. Except for the Boc group, the protective groups are, most conveniently, those which are not removed by mild acid treatment. These protective groups are removed by such methods as catalytic hydrogenation, sodium in liquid ammonia or HF treatment as known in the art.

If solid phase methods are used, the peptide is built up sequentially starting from the carboxy terminus and working toward the amino terminus of the peptide. Solid phase synthesis is begun by covalently attaching the C terminus of a protected amino acid to a suitable resin, such as a benzhydrylamine resin (BHA), methylbenzhydrylamine resin (MBHA) or chloromethyl resin (CMR), as is generally set forth in U.S. Patent No. 4,244,946. A BHA or MBHA support resin is used for the carboxy terminus of the product peptide is to be a carboxamide. A CMR support is generally used for the carboxy terminus if the produced peptide is to be a carboxyl group, although this may also be used to produce a carboxamide or ester.

Modification of the terminal amino group of the peptide is accomplished by alkylation or acetylation as is generally known in the art. These modifications may be carried out upon the amino acid prior to incorporation into the peptide, or upon the peptide after it has been synthesized and the terminal amino group liberated, but before the protecting groups have been removed.

Typically, acetylation is carried out upon the free amino group using the acyl halide, anhydride or activated ester, of the corresponding alkyl acid, in the presence of a tertiary amine. Mono-alkylation is carried out most conveniently by reductive alkylation of the amino group with an appropriate aliphatic aldehyde or ketone in the presence of a mild reducing agent, such as lithium or sodium cyanoborohydride. Dialkylation as well as quaternization may be carried by treating the amino group with an excess of an alkyl halide in the presence of a base.

Solution synthesis of peptides is accomplished using conventional methods used to form amide bonds. Typically, a protected Boc-amino acid which has a free carboxyl group is coupled to a protected amino acid which has a free amino group using a suitable carbodiimide coupling agent, such as N, N' dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-hydroxybenzotriazole (HOBT) and dimethylamino pyridine (DMAP). Other methods, such as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a protected Boc-amino acid, and subsequent reaction with the free amine of a protected amino acid, optionally in the presence of a base, are also suitable. For example, a protected Boc-amino acid or peptide is treated in an anhydrous solvent, such as methylene chloride or tetrahydrofuran (THF), in the presence of a base, such as N-methyl morpholine, or a trialkyl amine, with isobutyl chloroformate to form the

mixed anhydride, which is subsequently reacted with the free amine of a second protected amino acid or peptide. The peptide formed by these methods may be deprotected selectively, using conventional techniques, at the amino or carboxy terminus and coupled to other peptides or amino acids using similar techniques. After the peptide has been completed, the protecting groups may be removed as hereinbefore described, such as by hydrogenation in the presence of a palladium or platinum catalyst, treatment with sodium in liquid ammonia, hydrofluoric acid, trifluoroacetic acid or alkali.

Esters are often used to protect the terminal carboxyl group of peptides in solution synthesis. They may be converted to carboxylic acids by treatment with an alkali metal hydroxide or carbonate, such as potassium hydroxide or sodium carbonate, in an aqueous alcoholic solution. The acids may be converted to other esters via an activated acyl intermediate as previously described.

The amides and substituted amides of this invention are prepared from carboxylic acids of the peptides in much the same manner. Thus, ammonia or a substituted amine may be reacted with an activated acyl intermediate of an amino-protected α-amino acid or oligopeptide to produce the amide. Use of coupling reagents, such as DCC, is convenient for forming substituted amides from the carboxylic acid itself and a suitable amine.

In addition, the methyl esters of this invention may be converted to the amides, or substituted-amides, directly by treatment with ammonia, or a substituted amine, in methanol solution. A methanol solution of the methyl ester of the peptide is saturated with ammonia and stirred in a pressurized reactor to yield the simple carboxamide of the peptides. Procedures for the determination of the inhibition constant (Ki) by Dixon analysis are described in the art, e.g., in Dreyer, et al. Proc. Natl. Acad. Sci. U.S.A., 86, 9752-9756 (1989). A peptidolytic assay is employed using the substrate Ac-Arg-Ala-Ser-Gln-Asn-Tyr-Pro-Val-Val-NH_2 and recombinant HIV protease as in Stricker, et al., Proteins, 6, 134-154 (1989). The lower Ki value indicates a higher binding affinity.

Pharmaceutical compositions of the compounds of this invention, or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipient such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

A preferred composition for parenteral administration may additionally be comprised of a quantity of the compound encapsulated in a liposomal carrier. The liposome may be formed by dispersion of the compounds in an aqueous phase with phospholipids, with or without cholesterol, using a variety of techniques, including conventional handshaking, high pressure extrusion, reverse phase evaporation and microfluidization. A suitable method of making such compositions is more fully disclosed in copending Application Serial No. 06/763,484 and is incorporated herein by reference. Such a carrier may be optionally directed toward its site of action by an immunoglobulin or protein reactive with the viral particle or infected cells. The choice of such proteins would of course be dependent upon the antigenic determinants of the infecting virus. An example of such a protein is the CD-4 T-cell glycoprotein, or a derivative thereof, such as sCD-4 (soluble CD-4), which is reactive with the glycoprotein coat of the human immunodeficiency virus (HIV). Such proteins are disclosed in copending Application Serial No. 07/160,463, which is incorporated herein by reference. Similar targeting proteins could be devised, by methods known to the art, for other viruses and are considered within the scope of this invention.

Alternatively, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup or oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline and water. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glycerol monostearate or glycerol distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, a pulverized powder of the compounds of this invention may be combined with excipient such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository. The pulverized powders may also be compounded with an oily preparation, gel, cream or emulsion, buffered or unbuffered, and administered through a transdermal patch.

This invention is also a method for treating viral infection, particularly infection by retroviruses, which comprises administering a compound of formula I to a patient infected

with a susceptible virus. The method is particularly applicable to infection by the Human Immunodeficiency Virus, type 1. When the compounds of this invention are used to induce anti-viral activity in patients which are infected with susceptible viruses and require such treatment, the method of treatment comprises the administration orally, parenterally, bucally, trans-dermally, intravenously, intramuscularly, rectally or by insufflation, of an effective quantity of the chosen compound, preferably dispersed in a pharmaceutical carrier. Dosage units of the active ingredient are selected from the range of 0.05 to 50 mg/kg of body weight. Dosage units will typically be from 50 to 1000 mg. These dosage units may be administered one to ten times daily for acute or chronic infection. The dosage will be readily deterimined by one skilled in the art and will depend upon the age, weight and condition of the patient, and the route of administration. Combination therapy as described in Eur. Pat. Appl. No. 337 714 at pages 42-47 are included herein.

The Examples which follow serve to illustrate this invention. The Examples are intended to in no way limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

In the Examples, all temperatures are in degrees Celsius. Amino acid analyses were performed upon a Dionex Autoion 100. Analysis for peptide content is based upon Amino Acid Analysis. FAB mass spectra were performed upon a VG Aab mass spectrometer using fast atom bombardment. NMR spectra were recorded at 250 MHz using a Bruker Am 250 spectrometer. Multiplicities indicated are: s=singlet, d-doublet, t-triplet, q-quartet, m-multiplet and br indicates a broad signal.

Purification of Recombinant HIV Protease

Methods for expressing recombinant HIV protease in E.coli have bee described by Debouck, et al., Proc. Natl. Acad. Sci. USA, 84, 8903-6 (1987). The enzyme used to assay the compounds of this invention was produced in this manner and purified from the cell pellet as previously described by Stickler et al. Proteins, 6, 139-154 (1989).

EXAMPLES

Example 1

Preparation of (3S, 5S)-3,5-diamino-4-hydroxyheptane 1

Preparation by the Procedure of Scheme 1:

a) 1,2:4,5-dianhydro-D-(+)-arabitol 9

Benzyl trichloroacetimidate (29.1 mL, 201 mmol) was added to a solution of D-(+)-arabitol (13.9 g, 91.4 mmol; azeotropically dried with toluene) in dry acetonitrile (200 mL)

under Ar, and the mixture was stirred overnight. The solution was concentrated by rotary evaportion, dissolved in ethyl acetate (500 mL), washed with 5% $NaHCO_3$ (2x30 mL) and brine (30 mL), dired over Na_2SO_4 and concentrated. The residue was dissolved in dry THF (500 mL) and colled to -10°C, and solid sodium methylate (11.1 g, 205 mmol) was added with mechanical stirring under Ar. After 20 min the mixture was poured into ether (2.5 l), filtered through glass fiber filter paper to remove sodium methylate, and concentrated by rotary evaporation at 30°C. The residue was purified by flash chromatography (silica gel, 3:2 ether:pentane) to provide the titled compound 9 (3.96 g, 34.1 mmol, 37% yield).

b) 1,2:4,5-dianhydro-3-(O-benzyl)-D-(+)-arabitol 10

Benzyl bromide (8.92 mL, 75 mmol) was added to a slurry of NaH (1.8 g. 75 mmol) in THF (9 mL). The mixture was cooled to -10°C under Ar, and compound 9 (3.90 g, 34 mmol) in THF (9 mL) was added dropwise with stirring. The ice bath was removed, and the mixture was allowed to warm briefly to 40°C, then was recooled. The mixture was diluted with 1% acetic acid (100 mL), and extracted with ethyl acetate (2x250 mL). The organic extracts were washed with 5% $NaHCO_3$ (75 mL) and brine (75 mL), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue (gradient, 0-4% ethyl acetate in pentane) provided the titled compound 10 (3.88 g, 17.2 mmol, 55% yield). ^{1}HNMR ($CDCl_3$): δ 7.4-7.1(5H, m) 4.75(1H, d; J = 12 Hz), 4.65(1H, d; J = 12 Hz), 3.2(1H, m), 3.05(1H, m), 2.9(1H, t; J = 7 Hz), 2.8(2H, m), 2.65(2H, m).

c) (2S,4S)-1,5-Diazido-2,4-dihydroxy-3-benzyloxypentane 11

To 1.65 g (8.0 mmol) of compound 10 in 50 mL water and 50 mL dioxane was added 6.5 g (100 mmol) NaN3 and 340 mg (1 mmol) tetra-n-butylammonium bisulfate. The reaction mixture was heated under reflex for 4 hr, cooled, and concentrated to ca. 50 mL volume by rotary evaporation, and extracted with ethyl acetate (3x50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to an oil, which was combined with ether:hexane (1:1) and allowed to crystallize at 4°C to provie 1.76 g of titled compound 11 (69% yield). ^{1}HNMR ($CDCl_3$): δ 7.5-7.3(5H, m), 4.6(2H, dd; J = 12 Hz), 4.0(2H, m), 3.6-3.0(6H, m).

d) (2S,4S)-1,5-diazido-2,4-di-(methanesulfonyloxy)-3-benzyloxypentane 12

To 630 mg (2.15 mmol) of bisazide diol 11 in 6.0 mL of pyridine was added 350 µL (4.5 mmol) methanesulfonyl chloride at 0°C. The reaction mixture was allowed to warm to 25°C and stirred for 20 hr, then was diluted with 12 mL 6 N HCl, and extracted with 100 mL methylene chloride. The organic layer was washed with 3% NaHCO3, dried (Na_2SO_4)

and concentrated. Flash chromatography of the residue (95:5 CH2C12:ether) provided 867 mg (90% yield) of the titled compound **12**. ^{1}HNMR ($CDCl_3$): δ 7.4-7.2(5H, m), 5.0-4.7(4H, m), 4.02(2H dd, J = 3 Hz), 3.9-3.5(4H, m), 3.15(3H, s), 3.10(3H, s).

e) (2S,4S)-1,2:4,5-di-(N-carbonbenzyloxyimino)-3-benzyloxypentane **13**

To 310 mg (0.69 mmol) of the compound **12** of step (d) in 2 mL dry THF at 0°C was added 1.5 mL (1.5 mmol) 1 M $LiAlH_4$ in THF. The mixture was allowed to warm to 25°C and stirred overnight. Water (0.1 mL) was added, followed by 0.1 mL 15% NaOh and 0.4 mL water. The mixture was stirred vigorously with 10 mL ether and filtered. Concentration of the ether layer provided teh crude bisaziridine, which was dissolved in 5 mL CH_2Cl_2 and combined with 200 µL (1.4 mmol) triethylamine and 200 µL (1.4 mmol) of benzyl chloroformate. The mixture was stirred at 25°C for 3 hr, then filtered. The filtrate was concentrated and the residue was purified by flash chromatography (ethyl acetate:hexanes 1:5) to provide 89 mg (28% yield) of the titled compound **13**. ^{1}HNMR (400 MHz; $CDCl_3$): δ 7.4-7.2(15H, m), 5.0(1H, d; J = 12 Hz), 4.93(1H, d; J = 12 Hz), 4.88(1H, d; J = 12 Hz), 4.84(1H, d; J = 12 Hz), 4.74(1H, d; J = 12 Hz), 4.39(1H, d; J = 12 Hz), 2.82(1H, t; J = 6 Hz), 2.6(1H, m), 2.45(1H, m), 2.25(1H, d; J = 6 Hz), 2.15(1H, d; J = 6 Hz), 2.04(1H, d; J = 3 Hz), 2.02(1H, d; J = 3 Hz). MS (DCI, NH3): m/z 473.1(M+).

f) (3A,5S)-3,5-di-(carbonbenzyloxyamino)-4-benzyloxyheptane **14**

To a suspension of CuI (72 mg, 0.375 mmol) in 1.5 mL ether at -25°C was added 0.5 mL 1.5 M CH_3Li in ether. The resulting colorless solution was cooled to -45°C and a solution of bisaziridine **13** (10 mg, 0.02 mmol) in 0.5 mL ether was added. After stirring at -45°C for 1 hr, the mixture was allowed to warm to 10°C over a period of 6 hr, then was stirred for an additional 2 hr. The mixture was diulted with 2 mL saturated aqueous NH_4Cl and 1 mL saturated aqueous NH_3, then was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to provide the titled compound **14** (10 mg). ^{1}HNMR ($CDCl_3$): δ 7.2(15H, m), 5.2-4.9(4H, m), 4.93(1H, d; J = 12 Hz), 4.88(1H, d; J = 12 Hz), 4.84(1H, d; J = 12 Hz), 4.7(2H, d; J = 12 Hz), 4.4(2H, d; J = 12 Hz), 3.7(2H, m), 3.4(1H, d; J = 2 Hz), 1.6(4H, m), 1.0(3H, t; J = 7 Hz), 0.9(3H, t; J = 7 Hz).

g) (3S,5S)-3,5-diamino-4-hydroxyheptane **1**

The product of step (f) is stirred with 20% $Pd(OH)_2$ on carbon (50% by weight) in 0.1 N methanolic HCl under an atmosphere of hydrogen for 24 hr. Filtration and removal

of solvents provides the titled compound 1, as the dihydrochloride salt wherein X^1 and X^2 are hydrogen and R^1 and R^2 are ethyl.

Preparation by the Procedure of Scheme 2:

a) (3R,5R)-3,5-dihydroxy-4-benzyloxyheptane 15

To a suspension of CuI (143 mg, 0.75 mmol) in 3 mL ether at -35°C was added methyllithium (1 mL, 1.5 M in ether; 1.5 mmol). The resulting colorless solution was stirred at -30°C for 30 min, then cooled to -78°C. A solution of bisepoxide **10** (78 mg, 0.37 mmol) in 2 mL ether was added. The reaction was allowed to warm to 25°C over 4 hr, the saturated aqueous NH_4Cl and concentrated aquaous NH_3 were added. The mixture was extracted with ether, the organic layer was dried over Na_2SO_4 and the solvent was removed to furnish the titled compound (93 mg, 100% yield). ^{1}HNMR ($CDCl_3$): δ 7.4-7.1(5H, m), 4.7(1H, d; J = 12 Hz), 4.55(1H, d; J = 12 Hz), 3.9-3.7(2H, m), 3.2(1H, dd), 2.5(2H, b), 1.6-1.4(4H, m), 1.0(3H, t; J = 7 Hz), 0.9(3H, t; J = 7 Hz).

b). (3R,5R)-3,5-methanesulfonyloxy-4-benzyloxyheptane 16

Methanesulfonyl chloride (0.3 mL) was added dropwise to diol **15** (93mg) in pyridine (1mL) at 0°C. The mixture was allowed to warm to 25°C. After 12 hr the mixture was diluted with cold 6N HCl (10 mL) and extracted with CH_2Cl_2. The organic extract was washed with 3% $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to provide the titled compound (83 mg, 56% yield). ^{1}HNMR ($CDCl_3$): δ 7.4-7.2(5H, m), 4.75 (1H, m), 4.7(1H, d; J = 12 Hz), 4.6(1H, d; J = 12 Hz), 4.58(1H, m), 3.9(1H, dd; J = 2.6 Hz), 3.0(3H, s), 2.9(3H, s), 2.1-1.5(4H, m), 1.05(3H, t; J = 7 Hz), 1.0(3H, t; J = 7 Hz).

c). (3S, 5S)-3,5-diazido-4-benzyloxyheptane 17

A mixture of bismesylate **16** (83 mg. 0.21 mmol) and sodium azide (0.5 g 7.7 mmol) in 1.5 mL dimethylformamide was heated to 70°C for 12 hr. After cooling, ethyl acetate (20 mL) was added and the mixture was filtered and concentrated. Flash chromatography of the residue provided the titled compound (54 mg, 90% yield). ^{1}HNMR ($CDCl_3$): δ 7.4-7.2(5H, m), 4.65 (2H, s), 3.5-3.2(3H, m), 2.0-1.5(4H, m), 1.1(3H, t; J = 6 Hz), 1.05(3H, t; J = 6 Hz).

d). (3S, 5S)-3,5-diamino-4-benzyloxyheptane 18

To 328 mg (1.14 mmol) bisazide **17** in 5 mL THF at 0°C was added 200 mg $LiAlH_4$. The mixture was allowed to warm to 25°C and was stirred for 5 hr. The reaction was quenched by addition of 0.5 mL 15% NaOH, stirred for 15 min, diluted with 150 mL

ether and filtered. Concentration of the filtrate provided the titled compound (278 mg, 100% yield). ^{1}HNMR ($CDCl_3$): δ 7.26(5H, m), 4.5 (2H, dd; J = 12Hz), 3.1 (1H, dd; J = 4.6 Hz), 2.9(1H, m), 2.75(1H, m), 1.8-1.0(10H, m), 0.9(3H, t; J = 7 Hz), 0.85(3H, t; J = Hz).

e) (3S, 5S)-3,5-diamino-4-hydroxyheptane 1

To the diamine product 18 (52 mg) in 4 mL methanol was added 50 mg 20% $Pd(OH)_2$ on carbon and 2 drops concentrated aqueous HCl. The mixture was stirred under an atmosphere of H_2 for 16 hr, then was filtered and concentrated to provide the titled compound 1 (53 mg) as the dihydrochloride salt. ^{1}HNMR (CD_3OD): δ 3.75(1H, dd; J = 4.7 Hz), 3.2-3.0(2H, m), 1.8-1.4(4H, m), 0.9(6H, t; J = 7 Hz).

Example 2

Preparation of (3S, 5S)-3,5-di-(alanylalanyl)amino-4-hydroxyheptane 2.

a) (3S,5S)-3,5-di-(carbobenzyloxyalanylalanyl)amino-4- benzyloxyheptane 19

To the diamine product 18 of Example 1, step (k) (87 mg, 0.37 mmol) in 6 mL DMF was added 221 mg (0.75 mmol) carbobenzyloxyalanylalanine, 115 mg (0.75 mmol) HOBT, and 154 mg (0.75 mmol) DCC. The mixture was stirred overnight, then was concentrated, taken up in ethyl acetate, filtered, washed with water and brine and dired ($MgSO_4$). Removal of solvent followed by MPLC (silica; 2% methanol in CH_2Cl_2) provided the titled compound (109 mg). ^{1}HNMR (DMSO-d_6): δ 8.0-7.2(21H, m), 5.0(4H, bs), 4.6(2H, dd; J = 12 Hz), 4.2(2H, m), 4.0(2H, m), 3.8(1H, m), 3.7(1H, m), 3.5(1H, dd; J = 4.7 Hz), 1.7-1.3(4H, m), 1.1(12H, m), 0.75(6H, t).

b) (3S,5S)-3,5-di-(alanylalanyl)amino-4-hydroxyheptane 2

To the product 19 of step (a) (4.5 mg) in 1 mL DMF was added 10 mg to 20% $Pd(OH)_2$ on carbon. The mixture was stirred under 1 atmosphere of H_2 for 6 hr, then was filtered and concentrated to provide the titled compound 2 (3 mg) wherein X^1 and X^2 are AlaAla and R^1 and R^2 are ethyl. ^{1}HNMR (CD_3OD): δ 4.3(2H, m), 3.8(2H, m), 3.7(1H, m), 3.5(1H, m), 1.8-1.2(16H, m), 0.8(6H, dt).

Example 3

Preparation of (3S,5S)-3,5-di-(carbobenzyloxyvalyl)amino-4-hydroxyheptane 3.

To 133 mg (0.5 mmol) Cbz-Val in 2 mL THF at -40°C was added 65 μL (0.5 mmol)of isobutylchloroformate. After stirring for 10 min a solution of 25 mg (0.17 mmol) diamine hydrochloride 1 and 50 μL NMM in 1 mL DMF was added. The mixture was

slowly warmed to 20°C and stirred overnight, then was diluted with ethyl acetate, washed with 5% HCl, 5% $NaHCO_3$, and brine and the organic layer was concentrated. The residue was purified by flash chromatography (ethyl acetate:hexanes) to provide the titled compound 3 (18 mg) wherein X^1 and X^2 are Cbz-Val and R^1 and R^2 are ethyl. ^{1}HNMR ($CDCl_3$): δ 7.5-7.3(10H, m), 6.9(1H,br d), 6.35(1H, br d), 5.5(H, br d), 5.25(1H, br d), 5.1(4H, br s), 4.0-3.1(6H, m), 2.4-2.1(2H, m), 2.0-1.4(4H, m), 1.0-0.8(18H, m). MS (FAB): m/z 613.2$(M+H)^+$.

Example 4

Preparation of (2S, 4S)-2,4-di-(alanylalanyl)amino-3-hydroxy-1,5-diphenylpentane 4.

a). (2R,4R)-2,4-dihydroxy-3-benzyloxy-1,5-diphenylpentane 20

To a suspension of CuI (191 mg, 1 mmol) in ether (5 mL) at -60°C was added phenyllithium (4.0 mL, 2.0 mmol; 0.5 M in ether; freshly prepared from bromobenzene and lithium wire). The mixture was warmed to -50°C, then recooled to -78°C. A solution of bisepoxide **10** (40 mg, 0.19 mmol) in ether (1 mL) was added. The mixture was allowed to warm to 25°C over 6 hr with stirring. After an additional 12 hr, the mixture was diluted with ether and washed with 20 mL of 1:1 concentrated aqueous ammonia:saturated NH_4CL. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by medium-pressure liquid chromatography (1:4 ethyl acetate:hexanes) to provide the titled compound **20** (22 mg, 30% yield) as a colorless solid. ^{1}HNMR ($CDCL_3$): δ 7.5-7.0)15H,m), 4.75(1H, d; J=12 Hz), 4.55(1H, d; J=12 Hx), 4.2(2H, m), 3.3(1H, m), 3.0-2.7(6H, m).

b) (2S,4S)-2,4-di-(alanylalanyl)amino-3-hydroxy-1,5-diphenylpentane 4

The titled compound 4 wherein X^1 and X^2 are AlaAla and R^1 and R^2 are $PhCH_2$ is prepared from compound **20** by the procedures of Example 2.

Example 5

Preparation of (4R,6R)-4,6-diamino-5-hydroxy-2,8-dimethyl-1,8-nonane' 5.

a). (4R,6R)-4,6-dihydroxy-5-benzyloxy-2,8-dimethyl-1,8-nondiene 21

To a suspension fo CuI (192 mg, 1.0 mmol) in ether (2 mL) at -60°C was added isopropenyllithium (5.2 mL, 2.0 mmol; 0.38 M in ether; freshly prepared from 2-bromopropene and lithium wire). The mixture was warmed to -45°C, then recooled to -78°C. A solution of bisepoxide **10** (60 mg, 0129 mmol) in ether (5 mL) was added. The mixture was allowed to warm to 0°C over 2 hr with stirring. The mixture was diluted with

ether and washed with 5 mL of 1:1 concentrated aqueous ammonia:saturated NH_4Cl. The organic layer was dried over $MgSO_4$ and concentrated to provide the titled compound 21 (81 mg, 96% yield) as a colorless solid. ^{1}HNMR ($CDCL_3$): δ 7.3(5H, m), 4.9(1H, bs), 4.85(1H, bs), 4.80(1H, bs), 4.65(1H, d; J=12 Hz), 4.58(1H, d; J=12 Hz), 4.0(2H, m), 3.3(1H, dd; J=2.5 Hz), 2.55(1H, d; J=6 Hz), 2.55(1H, d; J=4 Hz), 2.5-2.1(4H, m), 1.7(1H, s).

b) (4R,6R)-4,6-dihydroxy-5-benxyloxy-2,8-dimethylnonane 22

To the product 21 of step (a) (105 mg, 0.38 mmol) in CH_2Cl_2 (1 mL) was added 55 mg Ir(COD)Py(PCy)$_3PF_6$ (Crabtree catalyst). The mixture was stirred for 6 hr under 1 atmosphere H_2, then was filtered and concentrated to provide the titled compound 22 (110 mg, 100% yield). ^{1}HNMR ($CDCl_3$): δ 7.3(5H, m), 4.6(1H, dd; J=12 Hz), 4.0(2H, m), 3.1(1H, br s), 2.7(2H, br s), 2.0-1.1(6H, m), 1.0-0.8(12H, m).

c) (4R,6R)-4,6-di-(methanesulfonyloxy)-5-benxyloxy-2,8-dimethylnonane 23

Methanesulfonyl chloride (0.25 mL) was added dropwise to diol 22 (93 mg) in pyridine (1 mL) at 0°C. The mixture was allowed to warm to 25°C. After 10 hr the mixture was diluted with cold 6N HCl (10 mL) and extracted with CH_2Cl_2. The organic extract was washed with 3% $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to provide the titled compound 23 (210 mg). ^{1}HNMR ($CDCl_3$): δ 7.4(5H, m), 5.0(1H, d; J=12 Hz). 4.7(1H, m), 4.6(1H, d; J=12 Hz), 3.85(1Hx dd; J-4.7 Hx), 3.0(3H, s), 2.0(3H, s), 2.0-1.1(6H, m), 1.0-0.9(12H, m).

d) (4R,6R)-4,6-diazido-5-benzyloxy-2,8-dimethylnonane 24

To the product 23 of step (c) (210 mg) in 2 mL DMF was added 870 mg (15 mmol) NaN3. The mixture was heated to 70°C for 7 hr, then was cooled and diluted with ethyl acetate. The filtrate was concentrated and the residue was purified by MPLC (ethyl acetate:hexanes 1:20) to provide the titled compound 24 (52 mg). ^{1}HNMR ($CDCl_3$): δ 7.3(5H, m), 4.55(2H, dd; J-12 Hz), 3.4-3.15(3H, m), 2.0-1.1(6H, m), 1.0-0.75(12H, m).

e). (4S,6S)-4,6-diamino-5-benzyloxy-2,8-dimethylnonane 25

To the product 24 of step (d) (52 mg, 0.15 mmol) in THF (3 mL) was added 80 mg $LiAlH_4$ (2 mmol) at 0 °C. The mixture was stirred at 25 °C overnight, then was quenched with 1N NaOH and diluted with ether (50 mL). Filtration and concentration provided the titled compound 25 (44 mg) as a colorless oil. ^{1}HNMR ($CDCl_3$): δ 7.3(5H, m), 4.6(2H, dd; J = 12 Hz), 3.1(1H, m), 3.05-2.95(2H, m), 1.9-1.1(6H, m), 1.0-0.8(12H, m).

f) (4R,6R)-4,6-diamino-5-hydroxy-2,8-dimethyl-1,8-nonane diahydrochloride 5

To 165 mg of diamine 25 from step (e) in 10 mL methanol containing 5 drops of conc. HCl was added 100 mg 20% $Pd(OH)_2$ on carbon. The mixture was stirred overnight under 1 atm H_2, then was filtered and concentrated to provide the titled compounds 5 (75 mg) wherein X^1 and X^2 are hydrogen and R^1 and R^2 are isobutyl. ^{1}HNMR (CD_3OD): δ 3.7(1H, m), 3.2(1H, m), 1.8-1.0(6H, m), 0.99-0.8(12H, m).

Example 6

Preparation of (4R,6R)-4,6-di-(alanylalanyl)amino-5-hydroxy-2,8-dimethyl-1,8-nonane 6

a) (4R,6R)-4,6-di-(carbobenzyloxyalanylalanyl)amino-5-benzyloxy-2,8-dimethyl-1,8-nonane 26

To the product 25 of Example 5, step (e) (44 mg, 0.15 mmol) in 2 mL DMF was added 110 mg Cbz-AlaAla (0.375 mmol), 58 mg (0.375 mmol HOBT, and 72 mg (0.375 mmol) DCC. The mixture was stirred for 48 hr at 25 °C, then was diluted with 20 mL ethyl acetate and filtered. The filtrate was concentrated and the residue was purified by MPLC (gradient, 0-5% methanol in CH_2Cl_2) to provide the titled compound 26 (24 mg). ^{1}HNMR (CD_3OD): δ 8.0-7.2 (21H, m), 5.0 (4H, overlapping dd), 4.2 (2H, m), 4.0 (4H, m), 3.5 (1H, br s), 1.7-1.15(18H, m), 0.9-0.7(12H, br t).

(b) (4R, 6R)-4,6-Di-(alanylalanyl)amino-5-hydroxy-2,8-dimethyl -1,8-nonane 6

To the product 26 of step (a) (12 mg) in 2 mL DMF was added 50 mg of 20% $Pd(OH)_2$ on carbon. The mixture was stirred under 1 atmosphere of H2 for 10 hr, then was diluted with methanol, filtered and concentrated to provide the titled compound 6 (7.5 mg) wherein X^1 and X^2 are AlaAla and R^1 and R^2 are isobutyl. ^{1}HNMR (CD_3OD): δ 4.25 (2H, m), 3.8 (1H, m), 3.65 (2H, m), 3.1 (1H, br d), 1.6-1.1 18H, m), 0.7 (12H, br d).

Example 7

Preparation of (4R,6R)-4,6-di-carbobenzyloxy)amino-5-hydroxy-2,8-dimethyl-1,8-nonane 7.

To 6.0 mg of the bis-amine hydrochloride product 5 in 0.5 mL CH_2Cl_2 at 20°C were added 5 mL triethylamine and 10 mL benzyl chloroformate. After 3 hr stirring, the mixture was applied to a silica column and eluted with CH_2Cl_2 followed by ether to provide the titled compound 7 (4.6 mg) wherein X^1 and X^2 are Cbz and R^1 and R^2 are isobutyl. ^{1}HNMR ($CDCl_3$): δ 7.3 (10H, bs), 5.1-4.9(6H, m), 3.9-3.7(2H, m), 3.5-

3.35(2H, m; 1H exchangeable with D_2O), 1.7-1.5(4H, m), 1.3-1.2(2H, m), 1.1-0.8(12H, m).

Example 8

Preparation of (4R,6R)-4,6-di-(carbobenzyloxyvalyl)amino-5-hydroxy-2,8-dimethyl-1,8-nonane 8

The titled compound 8 wherein X^1 and X^2 are Cbz-Val and R^1 and R^2 are isobutyl was prepared by the procedure of Example 3, except using compound 5 in place of compound 1. ^{1}NMR (250 MHz,$CDCl_3$) 7.5-7.28 (m, 10H), 6.8 (br s, 1H), 6.3 (br d, 1H), 5.6 (br s, 1H), 5.25 (br d, 1H), 5.1 (br s, 4H), 4.5-3.5 (m, 6H), 1.5-2.5 (m, 6H), 0.6-1.0 (m, 24 H).

Example 9

Preparation of (2S,4S)-1,5-diphenyl,3-hydroxy-2,4-bis(benzyloxycarbonylaminovalinyl-amino)pentane 40.

a) 2R,4R)-1,2,4,5-dianhydro-3-benzyloxyarabitol 33

To a solution of 15.2 g (100 mmol) of D(+)-arabitol in 350 mL of pyridine cooled in an ice bath was added 38.8 g (203.5 mmol) of p-toluenesulfonyl chloride in small portions. Stirred for 3 h, warmed to room temperature, poured to 500 mL of ether. Ether layer separated, aqueous layer extracted with 800 mL of ether. The combined organic layers were washed with 400 mL of 3% sodium bicarbonate, dried over anhydrous magnesium sulfate and solvents removed in vacuo to give 34.17g (74%) of the ditosylate 32. ^{1}HNMR (CD_3COCD_3) δ 7.75 (d, 4 H, J= 7 Hz), 7.25 (d, 4 H, J= 7 Hz), 4.4-3.5 (m, 7 H), 3.2 (b, 3 H), 2.5 (s, 6H).

To 10 g (55-60% in oil, 230 mmol) of sodium hydride in 300 mL of THF was added at 0° a solution of the bistosylate 32 in 200 mL of THF and stirred vigorously for 1 h. The reaction mixture was treated with dropwise addition of 12 mL of benzyl bromide in 10 mL of THF and stirred at 0° for 1 h. Allowed to warm to room temperature and stirred overnight. Quenched with 50 mL of water. dropwise at 0°. Extracted with ether, washed with water, dried over anhydrous sodium sulfate and solvents removed in vacuo. The residual oil was filtered thro silica gel (first eluted with hexane to remove unreacted benzyl bromide and then ethyl acetate Hexane ,1:4) to yield 9.0 g of the bisepoxide as a slight oil. Further purification was acheived by flash chromatography (silica, ethyl acetate,hexane 1:10) to give 6.10 g of the diepoxide 33. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.4-7.1 (m, 5H), 4.75 (d, 1H, J= 12 Hz), 4.65 (d, 1 H, J= 12 Hz), 3.2 (m, 1H), 3.05 (m, 1 H), 2.9 (t, 1 H, J= 7 Hz), 2.8 (m, 2 H), 2. 65 (m, 2 H).

b) (2R,4R)-1,5-diphenyl,3-benzyloxy-2,4-dihydroxypentane 34

To a suspension of 2.99 g (15.5 mmol) of of copper(1) iodide in 30 mL of THF was added 18 mL of 1.8 M Phenyl lithium in cyclohexane ((freshly opened bottle). The reaction mixture was warmed to -50° and recooled to -78° and a solution of 1.01g (4.9 mmol) of the bisepoxide 33 in 10 mL of THF was added and allowed to warm to room temperature and stirred overnight. Processed as usual to give 1.75 g of of the diol 34 as an oil. Trituration with ether/hexane gave 1.45 g (82 %) of a colorless solid. Anal Calcd for $C_{24}H_{26}O_3$: C(79.53), H(7.23); Found: C(79.25), H(7.18); MS(DCI, NH_3) $(M+H)^+$ 364.5; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.4-6.8 (m, 15 H), 4.62 (d, 1 H, J= 12 Hz), 4.5 (d, 1 H, J= 12 Hz), 4.2 (m, 2 H), 3.3 (dd, 1 H, J=), 2.8 (m, 4 H).

c) (2R,4R)-1,5-diphenyl-3-benzyloxy-2,4-bis(methanesulfonyloxy)pentane 35 and (2S,4S)-1,5-diphenyl-3-benzyloxy-2,4-diazidopentane 36

To 400 mg of the diol in 5 mL of pyridine at 0° was added 1 mL of methane sulfonyl chloride and stirred for 18 h at room temperature. Poured into 20 mL of ice cold3 N hydrochloric acid extracted with 50 mL of methylene chloride, washed with 3 % sodium bicarbonate dried over anhydrous sodium sulfate and solvents removed in vacuo to give 1.20 g of 35 as an oil.

The above crude product was dissolved in 5 mL of DMSO and added 1.05 g (16 mmol) of sodium azide. The reaction mixture was heated at 80° for 6 h and then at 100° for an additional 8 h. The reaction was cooled, diluted with ether and unreacted sodium azide was filtered off. The combined solvents were removed in vacu and subjected to flash chromatography to give 285 mg of an inseparable mixture of monoazide 36, (2S,4S)-1,5-diphenyl-3-benzyloxy-4-azido-pent-1-ene, and bisazide 37 in the ratio 70: 30 as caclulated from ^{1}HNMR.

d) (2S,4S)-1,5-diphenyl,3-benzyloxy-2,4-diaminopentane 38

To 279 mg of the mixture of azide products (36+37) obtained above in 10 mL of diethyl ether at 0° was added 3 mL of a 1M solution of lithium aluminium hydride in THF over 10 min. Stirred at 0° for 30 min warmed to room temperature and stirred for 3 h. Cooled in an ice bath and quenched with 1 mL of 10% sodium hydroxide, diluted with ether and stirred for 2 h. The precipitate was filtered off through celite and washed with ether. Removal of solvents followed by chromatography on 10 g florisil (hexane, ethy acetate:hexane 1:4, then methano) gave 112 mg of pure diamine 38. ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.2 (m, 15 H), 4.7(d, 21 H, J= 12 Hz), 4.5 (d, 21H, J= 1 H), 4.1(m, 1H), 2.3-3.2 (m, 6 H).

e) (2S,4S)-1,5-diphenyl-3-hydroxy-2,4-diaminopentane 39

62 mg of the diamino compound was subjected to hydrogenation in 10 mL of methanol containing 75 mg of conc. hydrochloric acid over 25 mg of Pd/C. Stirred for 8 h, catalyst was filtered off and washed with methanol. Removal of solvents gave 68 mg of a solid which on trituration with hexane ether provided 48 mg of the pure diamine as the hydrochloride. ^{1}HNMR (CD_3OD, 250 MHz) δ 7.4-6.9 (m, 10 H), 4.1 (bd, 1H, J= 6 Hz), 3.5-3.7 (m, 2 H), 2.5-3.4 (m, 4 H).

f) (2S,4S)-1,5-diphenyl,3-hydroxy-2,4-bis(benzyloxycarbonylaminovalinyl-amino)pentane 40

The titled product was prepared by the mixed anhydride method from 37 mg (0.107 mmol) of the diamine hydrochloride, 150 mg of Cbz-Val, 98 μL of N-methyl morpholine and 80 μL of isobutyl chloroformate 68 mg of a white solid. Analytical samples were prepared by flash column chromatography (silica, 10% MeOH/CH_2Cl_2). MS(ES/MS) $(M-H)^+$ 735; ^{1}HNMR ($CDCl_3$, 250 MHz) δ 7.4-7.0 (m, 20 H), 6.1 (d, 1H, J= 7 Hz), 5.5 (d, 1H, J= 7 Hz), 5.0 (m, 8 H), 4.0 (m, 2 H), 3.6 (m, 2 H), 2.8-3.4 (m, 4 H), 2.2 (m, 1H), 1.85 (m, 1H), 0.9 (d, 3 H, J= 7 Hz), 0.86 (d, 3 H, J= 7 Hz), 0.7 (d, 3 H, J= 7 Hz), 0.55 (d, 3 H, J= 7 Hz).

Example 10

Preparation of (3S, 5S)-3,5-di-(carbobenzyloxyalanylalanyl)amino-4-hydroxyheptane 50.

a) (2R,4R)-1,5-diazido-2,4-dihydroxy-3-benzyloxypentane 41

To 1.65 g (8.0 mmol) of bisepoxide 33 in 50 mL water and 50 mL dioxane was added 6.5 g (100 mmol) NaN3 and 340 mg (1 mmol) tetra-n-butylammonium bisulfate. The reaction mixture was heated under reflux for 4 hr, cooled, and concentrated to ca. 50 mL volume by rotary evaporation, and extracted with ethyl acetate (3x50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to an oil, which was combined with with ether:hexane (1:1) and allowed to crystallize at 4°C to provide 1.76 g of the titled compound (69 % yield). ^{1}HNMR ($CDCl_3$): δ 7.5-7.3(5H, m), 4.6(2H, dd; J = 12 Hz), 4.0(2H, m), 3.6-3.0(6H, m).

b) (2R,4R)-1,5-diazido-2,4-di-(methanesulfonyloxy)-3-benzyloxypentane 42

To 630 mg (2.15 mmol) of bisazido diol 41 in 6.0 mL of pyridine was added 350 μL (4.5 mmol) methanesulfonyl chloride at 0°C. The reaction mixture was allowed to warm to 25°C and stirred for 20 hr, then was diluted with 12 mL 6 N HCl, and extracted

with 100 mL methylene chloride. The organic layer was washed with 3% NaHCO3, dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (95:5 CH_2Cl_2:ether) provided 867 mg (90% yield) of the titled compound. ^{1}HNMR ($CDCl_3$): δ 7.4-7.2(5H, m), 5.0-4.7(4H, m), 4.02(2H, dd, J = 3 Hz), 3.9-3.5(4H, m), 3.15(3H, s), 3.10(3H, s).

c) (2S,4S)-1,2:4,5-di-(N-carbobenzyloxyimino)-3-benzyloxypentane 43

To 310 mg (0.69 mmol) of the compound 42 in 2 mL dry THF at 0°C was added 1.5 mL (1.5 mmol) 1 M $LiAlH_4$ in THF. The mixture was allowed to warm to 25°C and stirred overnight. Water (0.1 mL) was added, followed by 0.1 mL 15% NaOH and 0.4 mL water. The mixture was stirred vigorously with 10 mL ether and filtered. Concentration of the ether layer provided the crude bisaziridine, which was dissolved in 5 mL CH_2Cl_2 and combined with 200 µL (1.4 mmol) triethylamine and 200 µL (1.4 mmol) of benzyl chloroformate. The mixture was stirred at 25°C for 3 hr, then filtered. The filtrate was concentrated and the residue was purified by flash chromatography (ethyl acetate:hexanes 1:5) to provide 89 mg (28% yield) of the titled compound. ^{1}HNMR (400 MHz; $CDCl_3$): δ 7.4-7.2(15H, m), 5.0(1H, d; J = 12 Hz), 4.93(1H, d; J = 12 Hz), 4.88(1H, d; J = 12 Hz), 4.84(1H, d; J = 12 Hz), 4.74(1H, d; J = 12 Hz), 4.39(1H, d; J = 12 Hz), 2.82(1H, t; J = 6 Hz), 2.6(1H, m), 2.45(1H, m), 2.25(1H, d; J = 6 Hz), 2.15(1H, d; J = 6 Hz), 2.04(1H, d; J = 3 Hz), 2.02(1H, d; J = 3 Hz). MS (DCI, NH3): m/z 473.1(M^+).

d) (3S, 5S)-3,5-di-(carbobenzyloxyamino)-4-benzyloxyheptane 44

To a suspension of CuI (72 mg, 0.375 mmol) in 1.5 mL ether at -25°C was added 0.5 mL 1.5 M CH_3Li in ether. The resulting colorless solution was cooled to -45°C and a solution of bisaziridine 43 (10 mg,, 0.02 mmol) in 0.5 mL ether was added. After stirring at -45°C for 1 hr, the mixture was allowed to warm to 10°C over a period of 6 hr, them was stirred for an additional 2 hr. The mixture was diluted with 2 mL saturated aqueous NH_4Cl and 1 mL saturated aqueous NH_3, then was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to provide the titled compound (10 mg). ^{1}HNMR ($CDCl_3$): δ 7.2(15H, m), 5.2-4.9(4H, m), 4.93(1H, d; J = 12 Hz), 4.88(1H, d; J = 12 Hz), 4.84(1H, d; J = 12 Hz), 4.7(2H, d; J = 12 Hz), 4.4(2H, d; J = 12 Hz), 3.7(2H, m), 3.4(1H, d; J = 2 Hz), 1.6(4H, m), 1.0(3H, t; J = 7 Hz), 0.9(3H, t; J = 7 Hz). MS(DCI,NH_3)

$(M+H)^+$ 505.1

e) (3R, 5R)-3,5-dihydroxy-4-benzyloxyheptane 45

To a suspension of CuI (143 mg, 0.75 mmol) in 3 mL ether at -35°C was added methyllithium (1 mL, 1.5 M in ether; 1.5 mmol). The resulting colorless solution was

stirred at -30°C for 30 min, then cooled to -78°C. A solution of bisepoxide 33 (78 mg, 0.37 mmol) in 2 mL ether was added. The reaction was allowed to warm to 25°C over 4 hr, the saturated aqueous NH_4Cl and concentrated aqueous NH_3 were added. The mixture was extracted with ether, the organic layer was dried obver Na_2SO_4 and the solvent was removed furnish the titled compound (93 mg, 100% yield). ^{1}HNMR ($CDCl_3$): δ 7.4-7.1(5H, m), 4.7(1H, d; J = 12 Hz), 4.55(1H, d; J = 12 Hz), 3.9-3.7(2H, m), 3.2(1H, dd), 2.5(2H, b), 1.6-1.4(4H, m), 1.0(3H, t; J = 7 Hz), 0.9(3H, t; J = 7 Hz); MS(DCI,NH_3) $(M+H)^+$ 239.2

f) (3R, 5R)-3,5-Methanesulfonyloxy-4-benzyloxyheptane 46

Methanesulfonyl chloride (0.3 mL) was added dropwise to diol 45 (93 mg) in pyridine (1 mL) at 0°C. The mixture was allowed to warm to 25°C. After 12 hr the mixture was diluted with cold 6N HCl (10 mL) and extracted with CH_2Cl_2. The organic extract was washed with 3% $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to provide the titled compound (83 mg, 56% yield). ^{1}HNMR ($CDCl_3$): δ 7.4-7.2(5H, m), 4.75 (1H, m), 4.7(1H, d; J = 12 Hz), 4.6(1H, d; J = 12 Hz), 4.58(1H, m), 3.9(1H, dd; J = 2.6 Hz), 3.0(3H, s), 2.9(3H, s), 2.1-1.5(4H, m), 1.05(3H, t; J = 7 Hz), 1.0(3H, t; J = 7 Hz).

g) (3S, 5S)-3,5-diazido-4-benzyloxyheptane 47

A mixture of bismesylate 46 (83 mg, 0.21 mmol) and sodium azide (0.50 g, 7.7 mmol) in 1.5 mL dimethylformamide was heated to 70°C for 12 hr. After cooling, ethyl acetate (20 mL) was added and the mixture was filtered and concentrated. Flash chromatography of the residue provided the titled compound (54 mg, 90% yield). ^{1}HNMR ($CDCl_3$): δ 7.4-7.2(5H, m), 4.65 (2H, s), 3.5-3.2(3H, m), 2.0-1.5(4H, m), 1.1(3H, t; J = 6 Hz), 1.05(3H, t; J = 6 Hz).

h) (3S, 5S)-3,5-diamino-4-benzyloxyheptane 48

To 328 mg (1.14 mmol) bisazide 47 from step (j) in 5 mL THF at 0°C was added 200 mg $LiAlH_4$. The mixture was allowed to warm to 25°C and was stirred for 5 hr. The reaction was quenched by addition of 0.5 mL 15% NaOH, stirred for 15 min, diluted with 150 mL ether and filtered. Concentration of the filtrate provided the titled compound (278 mg, 100% yield). ^{1}HNMR ($CDCl_3$): δ 7.26(5H, m), 4.5 (2H, dd; J = 12Hz), 3.1(1H, dd; J = 4.6 Hz), 2.9(1H, m), 2.75(1H, m), 1.8-1.0(10H, m), 0.9(3H, t; J = 7 Hz), 0.85(3H, t; J = 7 Hz).

i) (3S, 5S)-3,5-diamino-4-hydroxyheptane 49

52 mg of the diamine product 48 in 4 mL methanol was added 50 mg 20% $Pd(OH)_2$ on carbon and 2 drops concentrated aqueous HCl. The mixture was stirred under an atmosphere of H_2 for 16 hr, then was filtered and concentrated to provide the titled compound (53 mg) as the dihydrochloride salt. ^{1}HNMR (CD_3OD): δ 3.75(1H, dd; J = 4.7 Hz), 3.2-3.0(2H, m), 1.8-1.4(4H, m), 0.9(6H, t; J = 7 Hz).

j) (3S, 5S)-3,5-di-(carbobenzyloxyalanylalanyl)amino-4-hydroxyheptane 50

To the diamine product 49 (87 mg, 0.37 mmol) in 6 mL DMF was added 221 mg (0.75 mmol) carbobenzyloxyalanylalanine, 115 mg (0.75 mmol) HOBT, and 154 mg (0.75 mmol) DCC. The mixture was stirred overnight, then was concentrated, taken up in ethyl acetate, filtered, washed with water and brine and dried ($MgSO_4$). Removal of solvent followed by MPLC (silica; 2% methanol in CH_2Cl_2) provided the titled compound (109 mg). ^{1}HNMR (DMSO-d6): δ 8.0-7.2(21H, m), 5.0(4H, bs), 4.6(2H, dd; J = 12 Hz), 4.2(2H, m), 4.0(2H, m), 3.8(1H, m), 3.7(1H, m), 3.5(1H, dd; J = 4.7 Hz), 1.7-1.3(4H, m), 1.1(12H, m), 0.75(6H, t). MS(FAB) $(M+H)^+$ 789.3

Example 11

Preparation of (3S, 5S)-3,5-di-(alanylalanyl)amino-4-hydroxyheptane 51.

To the product 19 (4.5 mg) in 1 mL DMF was added 10 mg of 20% $Pd(OH)_2$ on carbon. The mixture was stirred under 1 atmosphere of H_2 for 6 hr, then was filtered and concentrated to provide the titled compound (3 mg). ^{1}HNMR (CD_3OD): δ 4.3(2H, m), 3.8(2H, m), 3.7(1H, m), 3.5(1H, m), 1.8-1.2(16H, m), 0.8(6H, dt).

Example 12

Preparation of (3S, 5S)-3,5-di-(carbobenzyloxyvalyl)amino-4-hydroxyheptane 52.

To 133 mg (0.5 mmol) Cbz-Val in 2 mL THF at -40°C was added 65 µL (0.5 mmol) of NMM and 65 µL (0.5 mmol)of isobutylchloroformate. After stirring for 10 min a solution of 25 mg (0.17 mmol) diamine hydrochloride 1 and 50 µL NMM in 1 mL DMF was added. The mixture was slowly warmed to 20°C and stirred overnight, then was diluted with ethyl acetate, washed with 5% HCl, 5% $NaHCO_3$, and brine and the organic layer was concentrated. The residue was purified by flash chromatography (ethyl acetate:hexanes) to provide the titled compound (18 mg). ^{1}HNMR ($CDCl_3$): δ 7.5-7.3(10H, m), 6.9(1H, bd), 6.35(1H, bd), 5.5(1H, bd), 5.25(1H, bd), 5.1(4H, bs), 4.0-3.1(6H, m), 2.4-2.1(2H, m), 2.0-1.4(4H, m), 1.0-0.8(18H, m). MS (FAB): m/z 613.2$(M+H)^+$.

Example 13

Preparation of (4S, 6S)-4,6-diamino-5-hydroxy-2,8-dimethyl-1,8-nonane dihydrochloride 58.

a) (4R, 6R)-4,6-dihydroxy-5-benzyloxy-2,8-dimethyl-1,8-nondiene 53

To a suspension of CuI (192 mg, 1.0 mmol) in ether (2 mL) at -60°C was added isopropenyllithium (5.2 mL, 2.0 mmol; 0.38 M in ether; freshly prepared from 2-bromopropene and lithium wire). The mixture was warmed to -45°C, then recooled to -78°C. A solution of bisepoxide 33 (60 mg, 0.29 mmol) in ether (5 mL) was added. The mixture was allowed to warm to 0°C over 2 hr with stirring. The mixture was diluted with ether and washed with 5 mL of 1:1 concentrated aqueous ammonia:saturated NH_4Cl. The organic layer was dried over $MgSO_4$ and concentrated to provide the titled compound (81 mg, 96% yield) as a colorless solid. ^{1}HNMR ($CDCl_3$): δ 7.3(5H, m), 4.9(1H, bs), 4.85(1H, bs), 4.80(1H, bs), 4.75(1H, bs), 4.65(1H, d; J = 12 Hz), 4.58(1H, d; J = 12 Hz), 4.0(2H, m), 3.3(1H, dd; J = 2.5 Hz), 2.55(1H, d; J = 6 Hz), 2.55(1H, d; J = 4 Hz), 2.5-2.1(4H, m), 1.7(1H, s). MS(DCI,NH_3) $(M+H)^+$ 291.4

b) (4R, 6R)-4,6-dihydroxy-5-benzyloxy-2,8-dimethylnonane 54

To the product 53 (105 mg, 0.38 mmol) in CH_2Cl_2 (1mL) was added 55 mg Ir(COD)Py(PCy)3PF_6 (Crabtree catalyst). The mixture was stirred for 6 hr under 1 atmosphere H_2, then was filtered and concentrated to provide the titled compound (110 mg, 100% yield). ^{1}HNMR ($CDCl_3$): δ 7.3(5H, m), 4.6(1H, dd; J = 12 Hz), 4.0(2H, m), 3.1(1H, bs), 2.7(2H, bs), 2.0-1.1(6H, m), 1.0-0.8(12H, m).
MS(DCI,NH_3) $(M+H)^+$ 295.4.

c) (4R, 6R)-4,6-Di-(methanesulfonyloxy)-5-benzyloxy-2,8-dimethylnonane 55

Methanesulfonyl chloride (0.25 mL) was added dropwise to diol 54 (93 mg) in pyridine (1 mL) at 0°C. The mixture was allowed to warm to 25°C. After 10 hr the mixture was diluted with cold 6N HCl (10 mL) and extracted with CH_2Cl_2. The organic extract was washed with 3% $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography to provide the titled compound (210 mg). ^{1}HNMR ($CDCl_3$): δ 7.4(5H, m), 5.0(1H, m), 4.8(1H, d; J = 12 Hz), 4.7(1H, m), 4.6(1H, d; J = 12 Hz), 3.85(1H, dd; J = 4.7 Hz), 3.0(3H, s), 2.9(3H, s), 2.0-1.1(6H, m), 1.0-0.9(12H, m).

d) (4R, 6R)-4,6-diazido-5-benzyloxy-2,8-dimethylnonane 56

To the product 55 (210 mg) in 2 mL DMF was added 870 mg (15 mmol) NaN_3. The mixture was heated to 70°C for 7 hr, then was cooled and diluted with ethyl acetate. The filtrate was concentrated and the residue was purified by MPLC (ethyl acetate:hexanes

1:20) to provide the titled compound (52 mg). ^{1}HNMR ($CDCl_3$): δ 7.3(5H, m), 4.55(2H, dd; J = 12 Hz), 3.4-3.15(3H, m), 2.0-1.1(6H, m), 1.0-0.75(12H, m).

e) (4S, 6S)-4,6-diamino-5-benzyloxy-2,8-dimethylnonane **57**

To the product **56** (52 mg, 0.15 mmol) in THF (3 mL) was added 80 mg $LiAlH_4$ (2 mmol) at 0°C. The mixture was stirred at 25°C overnight, then was quenched with 1N NaOH and diluted with ether (50 mL). Filtration and concentration provided the titled compound (44 mg) as a colorless oil. ^{1}HNMR ($CDCl_3$): δ 7.3(5H, m), 4.6(2H, dd; J = 12 Hz), 3.1(1H, m), 3.05-2.95(2H, m), 1.9-1.1(6H, m), 1.0-0.8(12H, m).

f) (4S, 6S)-4,6-diamino-5-hydroxy-2,8-dimethyl-1,8-nonane dihydrochloride **58**

To 165 mg of diamine **57** in 10 mL methanol containing 5 drops of conc. HCl was added 100 mg 20% $Pd(OH)_2$ on carbon. The mixture was stirred overnight under 1 atm H_2, then was filtered and concentrated to provide the titled compound (75 mg). ^{1}HNMR (CD_3OD): δ 3.7(1H, m), 3.35(1H, m), 3.2(1H, m), 1.8-1.0(6H, m), 0.99-0.8(12H,m). MS(DCI, NH_3) $(M+H)^+$ 203.2.

Example 14

Preparation of (4S,6S)-4,6-di-(carbobenzyloxyalanylalanyl)amino-5-hydroxy-2,8-dimethyl-1,8-nonane **59**

To the product **58** (44 mg, 0.15 mmol) in 2 mL DMF was added 110 mg Cbz-AlaAla (0.375 mmol), 58 mg (0.375 mmol) HOBT, and 72 mg (0.375 mmol) DCC. The mixture was stirred for 48 hr at 25°C, then was diluted with 20 mL ethyl acetate and filtered. The filtrate was concentrated and the residue was purified by MPLC (gradient, 0-5% methanol in CH_2Cl_2) to provide the titled compound (24 mg). ^{1}HNMR (CD_3OD): δ 8.0-7.2(21H, m), 5.0(4H, overlapping dd), 4.2(2H, m), 4.0(4H, m), 3.5 (1H, br s), 1.7-1.15(18H, m), 0.9-0.7(12H, br t).

Example 15

Preparation of (4S,6S)-4,6-di-(alanylalanyl)amino-5-hydroxy-2,8-dimethyl-1,8-nonane **60**.

To the product **59** (12 mg) in 2 mL DMF was added 50 mg of 20% $Pd(OH)_2$ on carbon. The mixture was stirred under 1 atmosphere of H_2 for 10 hr, then was diluted with methanol, filtered and concentrated to provide the titled compound (7.5 mg). ^{1}HNMR (CD_3OD): δ 4.25(2H, m), 3.8(1H, m), 3.65(2H, m), 3.1(1H, bd), 1.6-1.1(18H, m), 0.7(12H, bd). MS(FAB) $(M+H)^+$ 487.

Example 16

Preparation of (4S, 6S)-4,6-di-(carbobenzyloxy)amino-5-hydroxy-2,8-dimethyl-1,8-nonane 61.

To 6.0 mg of the bis-amine hydrochloride product 58 in 0.5 mL CH_2Cl_2 at 20°C were added 5 mL triethylamine and 10 mL benzyl chloroformate. After 3 hr stirring, the mixture was applied to a silica column and eluted with CH_2Cl_2 followed by ether to provide the titled compound (4.6 mg). ^{1}HNMR ($CDCl_3$): δ 7.3(10H, bs), 5.1-4.9 (6H, m), 3.9-3.7(2H, m), 3.5-3.35(2H, m; 1H exchangeable with D_2O), 1.7-1.5 (4H, m), 1.3-1.2 (2H, m), 1.1-0.8 (12H, m).

Example 17

Preparation of (2S, 4S)-2,4-di-(p-toluenesulfonyl)amino-3-hydroxy-1,5-diphenylpentane 62.

The titled product was prepared by sulfonylation of compound 40 (Example 9) with p-toluenesulfonyl chloride in methylene chloride and triethylamine. 1HNMR (250 MHz, CDCl3) 8.0-6.8 (m, 18H), 5.5 (d, 1H, J=7Hz), 5.2 (d, 1H, J=7Hz), 3.2-3.7 D(m, 4H), 2,4-2.7 (m, 4H), 2.5 (s, 3H), 2,45 (s, 3H).

Enzyme Inhibition

Inhibition of HIV protease activity

The inhibition assay has been previously described in Dreyer et al. Proc. Natl. Acad. Sci. USA, 86, 9752-9756 (1989) and Moore et al. Bioch. Bioph. Res. Com., 159, 420 (1989). A typical assay contained 10 mL MENDT buffer (50 mM Mes (pH 6.0; 2-(N-morpholino) ethanesulfonic acid), 1 mM EDTA, 1mM dithiothreitol, 200 mM NaCl, 0.1% Triton X-100); 2, 3, or 6 mM N-acetyl-L-arginyl-L-alanyl-L-seryl-L-glutaminyl-L-asparaginyl-L-tyrosyl-L-prolyl-L-valyl-L-valinamide (Ac-Arg-Ala-Ser-Gln-Asn-Tyr-Pro-Val-Val-NH_2; K_m = 7 mM); and micromolar and submicromolar concentrations of synthetic compounds. Following incubation at 37°C for several minutes, the reaction was initiated with 0.001-0.10mg purified HIV protease. Reaction mixtures (37°C) were quenched after 10-20 minutes with an equal volume of cold 0.6 N trichloroacetic acid, and, following centrifugation to remove precipitated material, peptidolysis products were analyzed by reverse phase HPLC (Beckman Ultrasphere ODS, 4.5 mm x 25 mm; mobile phase; 5-20% acetonitrile/H_2O - .1% TFA 915 min.), 20% acetonitrile/H_2O - .1% TFA (5 min) at 1.5 mL/min, detection at 220 nm. The elution positions of Ac-Arg-Ala-Ser-Gln-Asn-Tyr-Pro-Val-Val-NH2 (17-18 min) and Ac-Arg-Ala-Ser-Gln-Asn-Tyr (10-11 min) were confirmed with authentic material. Initial rates of Ac-Arg-Ala-Ser-Gln-Asn-Tyr formation were determined from integration of these peaks, and typically, the inhibitory

properties of the synthetic compounds were determined from slope/intercept analysis of a plot of 1/v vs. [inhibitor] (Dixon analysis). K_i values resulting from this type of primary analysis are accurate for competitive inhibitors only, and under conditions in which the Michaelis constant of the substrate used is well-determined.

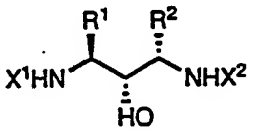
It is desirable for the compounds of this invention to have Ki values less than 50 μM, preferably less than 10 μM and more preferably less than 1 μM.

Following the procedures set forth herein and the teachings of the foregoing examples the compounds set forth in the following Table can be prepared having the structure and the substituent groups as designated therein.

Inhibition of rHIV-1 Protease

Compound	IC50
3	50
6	80
8	80
40	0.123
52	50
60	80
62	1,000

TABLE I



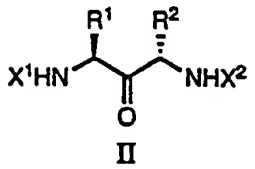
I

No.	X^1 and X^2	R^1 and R^2
1	H	ethyl
2	AlaAla	ethyl
3	Cbz-Val	ethyl
4	AlaAla	$PhCH_2$
5	H	i-Bu
6	AlaAla	i-Bu
7	Cbz-	i-Bu
8	Cbz-Val	i-Bu
101	Cbz-Ala	i-Bu
2	β-Ala	i-Bu

3	β-AlaVal	i-Bu
4	Cbz-AlaAla	i-Bu
105	BocAla	i-Bu
6	AcAlaAsn	i-Bu
7	AcGlnAsn	i-Bu
8	Cbz-PheAla	i-Bu
9	trifluoroAlaAla	i-Bu
110	Cbz-triflurorAlaAla	i-Bu
1	trifluoroAla	i-Bu
2	Cbz-trifluoroAla	i-Bu
3	$Ph(CH_2)_2CO$	i-Bu
4	Boc	i-Bu
115	Ac	i-Bu
6	$PhSo_2$	i-Bu
7	HCO	i-Bu
8	Propionyl	i-Bu
9	i-Butyryl	i-Bu
120	$Ph(CH_2)_2CO$	i-Bu
1	$PhSO_2Val$	i-Bu
2	Phenyllactoyl	i-Bu
3	Phenyllactoyl-Val	i-Bu
4	Cbz-Ala	$PhCH_2$
125	Cbz-Val	i-Butenyl
6	Cbz-Val	2-Propenyl
7	Cbz-Val	3-Butenuyl
8	Cbz-Val	n-Pentyl
9	Cbz-Val	$Ph(CH_2)_2$-
130	Cbz-Val	Cyclohexyl-CH_2-
1	Cbz-Val	2-Napthyl-CH_2-
2	Cbz-Val	3-Napthyl-CH_2-
3	Cbz-Val	2-Butynyl
4	Cbz-Val	3-Indoylmethyl
135	Cbz-Val	trans-3-phenyl-3-propenyl
6	Cbz-Val	N-Piperidinyl-CH_2-
7	Cbz-Val	N-Morpholinyl-CH_2-
8	Cbz-Val	$(CH_3)_2N$-CH_2
9	Cbz-Val	t-ButylNH-CH_2-

140	Cbz-Val	N-Imidazoyl-CH_2
1	Cbz-Val	PhCONH-CH_2
2	Cbz-Val	N-Indoyl-CH_2
3	Cbz-Val	t-ButylCONH-CH_2
4	Cbz-Val	$BocNHCH_2$
145	Cbz-Val	NH_2CH_2
6	Cbz-Val	N-benzimidazolyl
7	Cbz-Val	$PhCH_2O$-CH_2
8	Cbz-Val	PhO-CH_2
9	Cbz-Val	$CH_3(CH_2)_2O$-CH_2
150	Cbz-Val	CH_3O-CH_2
1	Cbz-Val	$(CH_3)_2CHO$-CH_2
2	Cbz-Val	t-Butyl-O-CH_2
3	Cbz-Val	$(CH_3)_2CHCH_2O$-CH_2
4	Cbz-Val	$CH_3CH_2(CH_3)CHO$-CH_2
155	Cbz-Val	Cyclohexyl-O-CH_2
6	Cbz-Val	$PhCH_2OCH_2O$-CH_2
7	Cbz-Val	CH_3OCH_2O-CH_2
8	Cbz-Val	$CH_3OCH_2CH_2OCH_2OCH_2$
9	Cbz-Val	CH_3S-CH_2
160	Cbz-Val	PhS-CH_2
1	Cbz-Val	$(CH_3)_2CHS$-CH_2
2	Cbz-Val	$CH_3(CH_2)_2S$-CH_2
3	Cbz-Val	$CH_3(CH_2)_3S$-CH_2
4	Cbz-Val	$CH_3S(O)$-CH_2
165	Cbz-Val	$CH_3S(O)_2$-CH_2
6	Cbz-Val	$PhS(O)_2$-CH_2
7	Cbz-Val	i-Propyl-$S(O)_2$-CH_2
8	Cbz-Val	n-Propyl-$S(O)_2$-CH_2
9	Cbz-Val	n-Butyl-$S(O)_2$-CH_2
170	Cbz-Val	$(Ph_2O)_2P(O)$-CH_2
1	Cbz-Val	$(CH_3O)_2P(O)$-CH_2
2	Cbz-Val	$(n\text{-ButylO})_2P(O)$-CH_2
3	Cbz-Val	$(EtO)_2P(O)$-CH_2
4	Cbz-Ala	$(CH_3O)_2P(O)$-CH_2

TABLE II



II

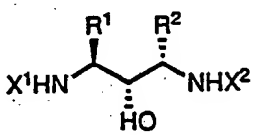
No.	X^1 and X^2	R^1 and R^2
1	H	ethyl
2	AlaAla	ethyl
3	Cbz-Val	ethyl
4	AlaAla	$PhCH_2$
5	H	i-Bu
6	AlaAla	i-Bu
7	Cbz-	i-Bu
8	Cbz-Val	i-Bu
201	Cbz-Ala	i-Bu
2	β-Ala	i-Bu
3	β-AlaVal	i-Bu
4	Cbz-AlaAla	i-Bu
205	BocAla	i-Bu
6	AcAlaAsn	i-Bu
7	AcGlnAsn	i-Bu
8	Cbz-PheAla	i-Bu
9	trifluoroAlaAla	i-Bu
210	Cbz-triflurorAlaAla	i-Bu
1	trifluoroAla	i-Bu
2	Cbz-trifluoroAla	i-Bu
3	$Ph(CH_2)_2CO$	i-Bu
4	Boc	i-Bu
215	Ac	i-Bu
6	$PhSo_2$	i-Bu
7	HCO	i-Bu
8	Propionyl	i-Bu
9	i-Butyryl	i-Bu
220	$Ph(CH_2)_2CO$	i-Bu
1	$PhSO_2Val$	i-Bu
2	Phenyllactoyl	i-Bu

3	Phenyllactoyl-Val	i-Bu
4	Cbz-Ala	$PhCH_2$
225	Cbz-Val	i-Butenyl
6	Cbz-Val	2-Propenyl
7	Cbz-Val	3-Butenuyl
8	Cbz-Val	n-Pentyl
9	Cbz-Val	$Ph(CH_2)_2$-
230	Cbz-Val	Cyclohexyl-CH_2-
1	Cbz-Val	2-Napthyl-CH_2-
2	Cbz-Val	3-Napthyl-CH_2-
3	Cbz-Val	2-Butynyl
4	Cbz-Val	3-Indoylmethyl
235	Cbz-Val	trans-3-phenyl-3-propenyl
6	Cbz-Val	N-Piperidinyl-CH_2-
7	Cbz-Val	N-Morpholinyl-CH_2-
8	Cbz-Val	$(CH_3)_2N$-CH_2
9	Cbz-Val	t-ButylNH-CH_2-
240	Cbz-Val	N-Imidazoyl-CH_2
1	Cbz-Val	PhCONH-CH_2
2	Cbz-Val	N-Indoyl-CH_2
3	Cbz-Val	t-ButylCONH-CH_2
4	Cbz-Val	$BocNHCH_2$
245	Cbz-Val	NH_2CH_2
6	Cbz-Val	N-benzimidazolyl
7	Cbz-Val	$PhCH_2O$-CH_2
8	Cbz-Val	PhO-CH_2
9	Cbz-Val	$CH_3(CH_2)_2O$-CH_2
250	Cbz-Val	CH_3O-CH_2
1	Cbz-Val	$(CH_3)_2CHO$-CH_2
2	Cbz-Val	t-Butyl-O-CH_2
3	Cbz-Val	$(CH_3)_2CHCH_2O$-CH_2
4	Cbz-Val	$CH_3CH_2(CH_3)CHO$-CH_2
255	Cbz-Val	Cyclohexyl-O-CH_2
6	Cbz-Val	$PhCH_2OCH_2O$-CH_2
7	Cbz-Val	CH_3OCH_2O-CH_2
8	Cbz-Val	$CH_3OCH_2CH_2OCH_2OCH_2$
9	Cbz-Val	CH_3S-CH_2

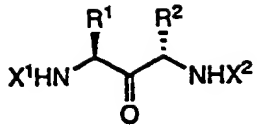
260	Cbz-Val	$PhS-CH_2$
1	Cbz-Val	$(CH_3)_2CHS-CH_2$
2	Cbz-Val	$CH_3(CH_2)_2S-CH_2$
3	Cbz-Val	$CH_3(CH_2)_3S-CH_2$
4	Cbz-Val	$CH_3S(O)-CH_2$
265	Cbz-Val	$CH_3S(O)_2-CH_2$
6	Cbz-Val	$PhS(O)_2-CH_2$
7	Cbz-Val	i-Propyl-$S(O)_2-CH_2$
8	Cbz-Val	n-Propyl-$S(O)_2-CH_2$
9	Cbz-Val	n-Butyl-$S(O)_2-CH_2$
270	Cbz-Val	$(Ph_2O)_2P(O)-CH_2$
1	Cbz-Val	$(CH_3O)_2P(O)-CH_2$
2	Cbz-Val	$(n\text{-}ButylO)_2P(O)-CH_2$
3	Cbz-Val	$(EtO)_2P(O)-CH_2$
4	Cbz-Ala	$(CH_3O)_2P(O)-CH_2$

Claims:

1. A compound of the formula I or II:



I



II

wherein X^1 and X^2 are the same or different and are A-$(B)_n$- where n = 0-2; and

B is, independently, an α-amino acid chosen from the group: Ala, Asn, Cys, Trp, Gly, Gln, Ile, Leu, Met, Phe, Pro, Ser, Thr, Tyr, Val, His, or trifluoroalanine, wherein the amino group of B is bonded to A or the carboxy group of the adjacent residue B, whichever is appropriate, and the carboxy group of B is bonded to the amino group of the adjacent residue B or I or II, whichever is appropriate; and

A is covalently attached to the amine group of the adjacent residue B or to the amine group of I or II if n=0, and is:

1) trityl,
2) hydrogen,
3) C_1-C_6 alkyl,
4) R^3-CO- wherein R^3 is:
   a) hydrogen,
   b) C_1 - C_6 alkyl, unsubstituted or substituted with one or more hydroxyl groups, chlorine atoms, or fluorine atoms,
   c) phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4, wherein R^4 is:
      i) C_1 - C_4 alkyl,
      ii) halogen, whrein halogen is F, Cl, Br or I,
      iii) hydroxyl,
      iv) nitro,
      v) C_1 - C_3 alkoxy, or
      vi) -CO-N$(R^{10})_2$ wherein R^{10} is, independently, H or C_1-C_4alkyl;
   d) a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazolyl;
5) phthaloyl wherein the aromatic ring is unsubstituted or substituted with one or more substitutents R^4,
6) $R^5(R^6R^7C)_m$-CO- wherein m = 1-3 and R^5, R^6, and R^7 are independently:
   a) hydrogen,
   b) chlorine or fluorine,

c) C_1 - C_3 alkyl unsubstituted or substituted with ne or more chlorine or fluorine atoms or hydroxyl groups,

d) hydroxyl,

e) phenyl or naphthyl unsubstituted or substituted with one or more substitutents R^4,

f) C_1 - C_4 alkoxy,

g) a 5-7 member heterocycle,

h) R^5, R^6, and R^7 may be independently joined to form a monocyclic, bicyclic, or tricyclic ring system each ring of which is C_3-C_6 cycloalkyl;

7) $R^5(R^6R^7C)_mW$- wherein m = 1-3 and W is OCO or SO_2 and R^5, R^6, and R^7 are as defined above, except R^5, R^6, and R^7 are not chlorine, fluorine or hydroxyl if they are adjacent to W;

8) R^8-W- wherein R^8 is a 5-7 member heterocycle such as pyridyl, furyl, or benzisoxazoyl;

9) R^9-W- wherein R^9 is phenyl or naphthyl unsubstituted or substituted with one or more substituents R^4;

10) R^5-$(R^6R^7C)_m$-$P(O)(OR^{11})$- wherein R^{11} is C_1 - C_4 alkyl or phenyl;

11) R^8-$P(O)(OR^{11})$-; or

12) R^9-$P(O)(OR^{11})$-;

R^1 and R^2 are the same or different and are:

1) $-CH_2R^{12}$ wherein R^{12} is

a) NH-A wherein A is defined as above;

b) R^5-$(R^6R^7C)_m$-;

c) R^5-$(R^6R^7C)_mV$- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-$(R^6R^7C)_m$-$S(O)_n$- wherein m = 1-3 and n = 0-2 and R^5, R^6, and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to sulfur,

e) R^8-$S(O)_n$-,

f) R^9-$S(O)_n$-,

g) $(R^{13}O)P(O)(OR^{14})$- wherein R^{13} and R^{14} are, independently:

i) C_1 - C_6 alkyl,

ii) C_3 - C_6 cycloalkyl,

iii) H,

iv) R^9,

v) R^8,

h) $R^{13}P(O)(OR^{14})$-,

i) $N(R^{10})_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogenous heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl,

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C_1 - C_6 alkyl,

ii) R^9,

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH_2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-Benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2 - C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2 - C_6 alkenyl, optinally substituted with one or more gropus R^9;

2) hydrogen,

3) C_1 - C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups,

4) C_3 - C_7 cycloalkyl; and pharmaceutically acceptable salts thereof.

2. A compound as defined in claim 1 wherein the compound has the structure I and wherein $R^1 = R^2$ and $X^1 = X^2$.

3. A compound as defined in claim 2 wherein R^1 and R^2 are C_1-C_6alkyl.

4. A compound as defined in claim 2 wherein R^1 and R^2 are benzyl.

5. A compound as defined in claims 1-4 wherein X^1 and X^2 are selected from AlaAla, Val, Cbz-Val, Cbz or hydrogen.

6. A compound of claim 1 wherein the protease activity inhibitor constant Ki is less than about 10 μM.

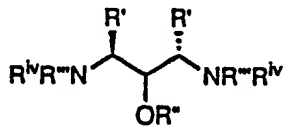
7. A compound according to claim 1 for use in a medicament.

8. A pharmaceutical composition comprising a compound according to claim 1 and a pharmacetically acceptable carrier.

9. A method of treating infection by a retrovirus which comprises administering a compound according to claim 1.

10. A method according to claim 9 wherein the retrovirus is the Human Immunodeficiency Virus type 1.

11. A process for preparing a compound of the formula:



wherein R' is

1) a) NH-A wherein A, R^5- R^{10} and m are as defined in claim 1;

b) R^5-$(R^6R^7C)_m$-;

c) R^5-$(R^6R^7C)_m$ V- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-$(R^6R^7C)_m$-S- wherein m = 1-3, and R^5, R^6, and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to sulfur,

e) R^8-S-,

f) R^9-S-,

g) $(R^{13}O)P(O)(OR^{14})$- wherein R^{13} and R^{14} are, independently:

i) C_1-C_6 alkyl,

ii) C_3-C_6 cycloalkyl,

iii) H,

iv) R^9, or

v) R^8,

h) $R^{13}P(O)(OR^{14})$-,

i) $N(R^{10})_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogens heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl, or

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C^1-C^6 alkyl,

ii) R^9, or

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4;

n) N-benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2-C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2-C_6 alkenyl, optionally substituted with one or more groups R^9;

2) hydrogen,

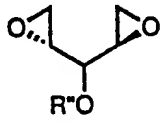
3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups, or

4) C_3-C_7 cycloalkyl;

R" is a hydroxyl protecting group, R"' and R'' are hydrogen, an amino-protecting group or taken together are N_2,

which comprises

1) reacting a compound of the formula:

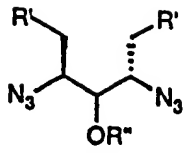


with a compound R'-Z, wherein Z is a moiety which renders R' nucleophilic,

2) converting the resulting hydroxy groups to displaceable groups, and

3) reacting the displaceable groups with a nitrogen nucleophile.

12. A compound of the formula:



III

wherein R' is:

1) a) NH-A wherein A, R^5 - R^{10} and m are as defined in claim 1;

b) R^5-(R^6R^7C)$_m$-;

c) R^5-(R^6R^7C)$_m$ V- wherein V is O or NH, except R^5, R^6 and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to V,

d) R^5-(R^6R^7C)$_m$-S- wherein m = 1-3, and R^5, R^6, and R^7 are as defined above except R^5, R^6, and R^7 are not hydroxyl, chlorine or fluorine if they are adjacent to sulfur,

e) R^8-S-,

f) R^9-S-,

g) (R^{13}O)P(O)(OR^{14})- wherein R^{13} and R^{14} are, independently:

i) C_1-C_6 alkyl,

ii) C_3-C_6 cycloalkyl,

iii) H,

iv) R^9, or

v) R^8,

h) R^{13}P(O)(OR^{14})-,

i) N(R^{10})$_2$,

j) $NR^{15}R^{16}$ wherein R^{15} and R^{16} are joined to form a 4-6 membered saturated nitrogens heterocycle including:

i) azetidinyl,

ii) pyrrolidinyl,

iii) piperidinyl, or

iv) morpholinyl,

k) $R^{17}OCH_2O$ wherein R^{17} is:

i) C^1-C^6 alkyl,

ii) R^9, or

iii) CH_2Ar wherein Ar is phenyl, naphthyl or a 5-7 membered heterocycle,

l) $R^{17}OCH_2CH_2OCH2$,

m) N-imidazolyl where the imidazole ring is unsubstituted or substituted by a substituent R^4,

n) N-benzimidazolyl where the fused benzene ring is unsubstituted or substituted by one or more substituents R^4;

o) C_2-C_6 alkynyl, optionally substituted with one or more groups R^9; or

p) C_2-C_6 alkenyl, optionally substituted with one or more groups R^9;

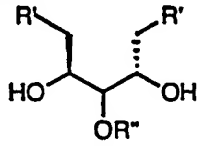
2) hydrogen,

3) C_1-C_6 alkyl, unsubstituted or substituted with one or more chlorine or fluorine atoms or hydroxyl groups, or

4) C_3-C_7 cycloalkyl; and

R" is a hydroxyl protecting group.

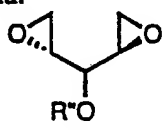
13. A compound of the formula:



IV

wherein R' and R" are as defined in claim 12.

14. A compound of the formula:



V

wherein R" is a hydroxyl protecting group.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/04757

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 37/00; 37/02; C07K 5/00; 7/00
U.S. Cl: 514/18, 19; 530/330, 331

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.Cl:	514/18, 19; 530/330, 331

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y,P	EP, A, 0,402,646 (KEMPF ET AL) 19 December 1990, See entire document.	1-14
Y	J. Med. Chem., Volume 33, No. 10, issued 1990, Kempf et al., "Structure-Based, C2 Symmetric Inhibitors of HIV Protease," page 2687-89, see entire document.	1-14
Y,P	Science, volume 249, issued 03 August 1990, Erickson et al., "Design Activity, and 2.8 A Crystal Structure of a C2 Symmetric Inhibitor Complexed to HIV-1 Protease," page 527-533, see entire document.	1-14
Y	EP, A, 0,337,714 (SIGAL ET AL) 18 October 1989, see entire document.	1-14
Y	EP, A, 0, 357,332 (SIGAL ET AL) 07 March 1990, see entire document.	1-14

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 October 1991	14 NOV 1991
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Eric J. Kraus

FURTHER INF RMATION C NTINUED FROM THE SECOND SHEET

A	US, A, 4,661,473 (BOGER ET AL) 28 April 1987, See entire document.	1-14

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . . . . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.